U. S. DEPARTMENT OF AGRICULTURE.

BUREAU OF PLANT INDUSTRY—BULLETIN NO. 121.

B. T. GALLOWAY, *Chief of Bureau.*

MISCELLANEOUS PAPERS.

I. THE SUPPOSED RELATIONSHIP OF WHITE SNAKEROOT TO MILKSICKNESS, OR "TREMBLES."

By ALBERT C. CRAWFORD, *Pharmacologist, Poisonous-Plant Investigations.*

II MOUNTAIN LAUREL, A POISONOUS PLANT.

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III. RESULTS OF LOCO-WEED INVESTIGATIONS IN THE FIELD.

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By W. M. SCOTT, *Pathologist,* and JAMES B. RORER, *Assistant Pathologist, Investigations of Diseases of Fruits.*

VI. THE IMMUNITY OF THE JAPANESE CHESTNUT TO THE BARK DISEASE.

By HAVEN METCALF, *Pathologist in Charge of the Laboratory of Forest Pathology.*

ISSUED APRIL 18, 1908.

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MISCELLANEOUS PAPERS.

B. P. I.—321.

THE SUPPOSED RELATIONSHIP OF WHITE SNAKEROOT TO MILKSICKNESS, OR "TREMBLES."[a]

By ALBERT C. CRAWFORD, *Pharmacologist, Poisonous-Plant Investigations.*

HISTORICAL INTRODUCTION.

Many of the early settlers of the Ohio Valley, especially in Indiana and Illinois, were affected with a peculiar disorder known as milksickness, a disease which is said to have caused the death of Abraham Lincoln's mother. Persons with this disorder usually showed no mental disturbances save slight apathy, although late in the course of the disease there might be coma.

Milksickness was usually characterized by vomiting, which might be bloody, and obstinate constipation, but in rare cases this was absent.[b] So marked was this constipation that the name paralysis of the intestines was once suggested for the disorder.[c] The abdominal walls were retracted and the pulsations of the abdominal aorta could thus be easily seen. Later in the course of the disease tympanites has occurred.[d] The urinary secretion was diminished and the breath took on a peculiar fetid odor which was considered pathognomonic.

[a] One of the most serious diseases which formerly threatened the life of man and beast in the forested parts of the Ohio Valley and adjacent territory was that known as milksickness, or "trembles." Although of late years much less trouble has been experienced, an occasional outbreak is reported.

In responding to a request that the United States Department of Agriculture investigate an attack of milksickness occurring near Peoria, Ill., a favorable opportunity was obtained to test the widespread and persistent popular belief that the plant known as white snakeroot (*Eupatorium ageratoides* L. f.) is responsible for the trouble.

After a study extending through several months, Dr. Albert C. Crawford, Pharmacologist, acting under the direction of Dr. R. H. True, Physiologist in Charge of the Poisonous-Plant Investigations of this Bureau, has shown in the results summarized in this technical paper that the eating of the plant of the white snakeroot by animals or man is not followed by the disease and that there is probably no relation between them.—B. T. GALLOWAY, *Chief of Bureau.*

[b] Crookshank, N. On the "Sick Stomach" of the Western Country, or Gastro-enteritis. Phila. Jour. Med. and Phys. Sci., vol. 12, p. 254, 1826.

[c] Dawson, J. Causes and Treatment of Milksickness. Proc. Med. Convention, Ohio, 1842, p. 48.

[d] Wood, G. B. Treatise on the Practice of Medicine, vol. 1, p. 462, 1858.

Associated with these symptoms were those of prostration, with restlessness and great thirst. Pain was referred to various localities. The temperature usually remained normal or was subnormal, rarely exceeding 99° F.[a] At times it reached 100° F. There are, however, very few recorded cases in which the temperature was actually measured by a thermometer.[b] The pulse remained about normal, but might at times be accelerated. Nothing very characteristic was noted concerning the tongue save that it was enlarged.[c] In certain cases difficulty in swallowing was reported; in others hiccough was a more or less prominent symptom.[d] No reports were made as to the condition of the pupil or of any ocular disturbances save an intolerance of light.[e]

There was said to be an incubation period of from two to ten days,[f] although apparently some cases had no such period.[g] The disease itself usually lasted from two to twenty days, but chronic cases are reported.[h] The disorder generally occurred in spring or autumn, particularly in autumn, although it might appear at any season.[i] The conditions which were especially favorable for its development were said to be those which interfered with normal excretion.[j] One attack gave no immunity, but rather predisposed to a second one.[k]

The post-mortem records are few in number. The only lesions reported are those of irritation and inflammation of the stomach and

[a] Kimmell, J. A. Milk Sickness in America. Verhandl. d. X internat. med. Cong., vol. 2, pt. 5, p. 54, 1891.

[b] Hurd, A. Milk Sickness. Clinic, Cincinnati, vol. 9, p. 280, 1875.—Way, J. H. Clinical History, Nature and Treatment of "Milk-Sickness." Amer. Jour. Med. Sci., n. s., vol. 106, p. 310, 1893.—Yandell, L. P. Inquiry into the Nature of the Disease Called Milk-Sickness. West. Jour. Med. and Surg., 3 s., vol. 9, p. 393, 1852.—Drake, D. Memoir on the Disease Called by the People "Trembles." West. Jour. Med. and Surg., vol. 3, p. 178, 1841.

[c] Graff, G. B. On the Milk Sickness of the West. Amer. Jour. Med. Sci., n. s., vol. 1, p. 354, 1841.

[d] Coleman, A. Observations on the Disease Generally Known by the Name of the Sick Stomach. Phila. Jour. Med. and Phys. Sci., vol. 4, p. 325, 1822.

[e] Graff, G. B., l. c., p. 354.

[f] Beach, W. M. Milk Sickness. Trans. Ohio State Med. Soc., vol. 38, pp. 131, 133, 1884.—Kimmel, J. A., l. c., p. 50.

[g] Yandell, L. P., l. c., p. 394.

[h] Yandell, L. P., l. c., p. 392.—Kimmell, J. A., l. c., p. 54.

[i] Byford, W. H. Milk Sickness. Nashville Jour. Med. and Surg., vol. 9, p. 467, 1855.—Yandell, L. P., l. c., p. 379.—Beck, J. C. Milk-Sickness. North-West. Med. and Surg. Jour., vol. 14, p. 497, 1857.

[j] Philips, W. H. Milk Sickness. Cincinnati Lancet and Observer, vol. 38, p. 142, 1877.

[k] Philips, W. H., l. c., p. 147.—Yandell, L. P., l. c., p. 392.

intestines,[a] as shown by hemorrhages into the lumen of these organs and injection of their walls, with at times adhesion of the intestinal walls to one another.[b] The pyloric region was found contracted,[c] and Peyer's and Brunner's glands were swollen. Graff has reported in one case adhesions and thickening of the cerebral membranes.[d] In other cases in which autopsies were made very slight lesions were noted.[e]

The clinical symptoms of some cases of milksickness resemble closely those described by Vaughan and Novy under the name galactotoxismus[f] and would probably be so diagnosed if they occurred outside of the areas where milksickness is prevalent. Schmidt[g] suggested that cases of milksickness occurred in cities, but were not diagnosed as such. Other cases resemble other forms of ptomaine poisoning described by Vaughan,[h] while the symptoms of still others resemble those occurring in Van Ermengem's cases of sausage poisoning. These cases described by Van Ermengem[i] showed marked nausea and vomiting and severe constipation, although two cases had diarrhea. There was retention of urine, while the temperature, pulse, and mental symptoms remained about normal, as in cases of milksickness. Some difficulty in swallowing was noted and there were ocular disturbances—diplopia, dilatation of the pupil, ptosis, etc. The post-mortem examination, as in milksickness, showed no char-

[a] De Bruler, J. P. Milk-Sickness. Chicago Med. Jour., vol. 15, p. 209, 1858.

[b] Davis, K. H. Milk-Sickness. Atlanta Med. Reg., vol. 1, p. 394, 1881–82.

[c] Byford, W. H., l. c., p. 465.—Drake, D. Morbid Anatomy of Milksickness. West. Jour. Med. and Surg., vol. 4, 1841, p. 234.

[d] Graff, G. B., l. c., p. 366.

[e] Crookshank, N., l. c., p. 256.

[f] Vaughan, V. C., and Novy, F. G. Cellular Toxins, 1902, p. 216. Compare Graff, G. B., l. c., p. 364; also Walker, J. W., Milk-Sickness, Science, vol. 8, p. 483, 1886.

[g] Schmidt, C. H. Milk Sickness. Cincinnati Lancet and Observer, vol. 20, p. 412, 1877.

[h] Vaughan, V. C. Ptomaïnes, Toxins and Leucomaïns. Twentieth Century Practice, vol. 13.

[i] Van Ermengem, E. Ueber einem neuen anaerob. Bacillus u. seine Beziehungen z. Botulismus. Zeits. f. Hygiene, vol. 26, p. 1, 1897; Untersuch. ü. Fälle v. Fleischvergift. mit Symptomen v. Botulismus. Cent. f. Bakter., part 1, vol. 19, p. 442, 1896.—Römer, P. Ein Beitrag z. Aetiologie des Botulismus. Cent. f. Bakter., part 1, vol. 27, p. 857, 1900.—Kempner, W., and Pollack, B. Wirkung des Botulismustoxins (Fleischgiftes) und seines specifischen Antitoxins auf die Nervenzellen. Deutsch. Med. Woch., vol. 23, p. 505, 1897.—Brieger and Kempner, W. Beitr. z. Lehre von der Fleischvergift. Deutsch. Med. Woch., 1897, p. 521.—Kempner, W. Weiterer Beitrag z. Lehre von den Fleischvergift. Das Antitoxin des Botulismus. Zeits. f. Hygiene, vol. 26, p. 481, 1897.—Osler, W. Modern Medicine, vol. 1, p. 232, 1907.

acteristic macroscopic lesion. From the spleen was isolated an anaerobic bacillus which could reproduce the symptoms of the disorder in animals. This organism was found in various places in the meat used in making the sausage. On culture media it developed an odor of butyric acid. The toxin obtained from these cultures would resist heating at 70° C. for a short time, but heating to 100° C. destroyed it at once. Van Ermengem mentions that in cats injected with this toxin there was muscular rigidity and that the ocular symptoms in these animals were not marked. Dogs, however, were very resistant to the action of this toxin. This organism has also been found in the faeces of hogs. A similar outbreak occurred in Darmstadt after eating vegetables infected with the same organism.[a]

No doubt the term "milksickness" has been made to embrace a variety of clinical conditions; in fact, there has been such confusion in the reports that some authors, as Yandell, have denied its existence as a peculiar entity.[b]

The mortality as given by Coleman[c] is one death in every twenty or thirty cases. Others, as Mendenhall,[d] allude to milk-sickness as a "very grave disease"; others, again, speak of the outlook as favorable under the proper treatment.

In the same portions of the country in which milksickness occurred a similar, if not identical, disorder also affected domestic animals, especially cattle. In them muscular tremors were present and became especially noticeable when the animals were driven, so that this disorder received the name of "trembles."[e] It was also called the "tires," on account of the disinclination of the animals to move. A rigidity of the muscles has been noted by McCall.[f] The post-mortem examination showed the gastric mucosa to be softened and the stomach and intestines contracted,[g] in some cases gangrenous,[h] and at times there was more or less peritonitis. The odor developing at

[a] Fischer, A. Ueber eine Massenerkrankung an Botulismus infolge Genusses "verdorbener" Bohnenkonserven. Zeits. f. klin. Med., vol. 59, p. 58, 1906.

NOTE.—The bacillus *Aerogenes capsulatus* which occurs in the human intestinal tract may give rise to infections associated with constipation. See Herter, C. A., Common Bacterial Infections of the Digestive Tract, 1907, p. 207.

[b] Yandell, L. P., l. c., p. 398.—Hibberd, J. F. Observations on Milk-Sickness. Western Lancet, 1845, vol. 3, p. 448.

[c] Coleman, A., l. c., p. 325.

[d] Mendenhall, I. Milk-Sickness. Chicago Med. Jour., vol. 18, p. 435, 1861.

[e] Yandell, L. P., l. c., p. 398.

[f] McCall, A. Facts and Observations on the Milk Sickness. West. Jour. Med. and Phys. Sci., vol. 3, p. 467, 1830.

[g] Graff, G. B., l. c., p. 362.

[h] Dickey, W. Essay on Milk Sickness. Western Lancet, vol. 13, pp. 391–395, 1852.

some of these autopsies was especially offensive and was compared with the odor arising in mercurialism.[a] In one case the cerebral ventricles contained fibrin and the brain itself was surrounded by serum and pus.[b] The spinal cord in this case showed signs of inflammation. In other cases no special lesions were noted.[c]

It was proved that many cases of milksickness were communicated to man by means of milk and its products[d] or meat[e] obtained from cattle affected with the "trembles"; even the amount of cream usually added to coffee is said to have induced the disease.[f] Other cases apparently arose without the products of diseased animals being eaten, as by using contaminated water;[g] and, again, cases have occurred in vegetarians.[h] In some cases the fencing off of the suspected springs from the pasture was followed by the disappearance of "trembles" from the neighborhood. The "trembles" still appear at times, although much less common than formerly,[i] its disappearance being traced to the cultivation of the soil;[j] and it is associated with certain shady, sharply localized, wet, untilled areas. No characteristic geological peculiarity has been proved for these areas.[k] Drake met the disorder almost entirely on oak plateaus, and especially on the so-called "slashes" or marshy areas.[l] It is claimed that the

[a] Drake, D., l. c., p. 172.—McCall, A., l. c., p. 467.

[b] Graff, G. B., l. c., p. 363.

[c] Philips, W. H. Milksickness. Cincinnati Lancet and Observer, vol. 20, p. 132, 1887.—Beach, l. c., p. 137.

[d] Drake, D., l. c., p. 194.—Wilkinson, G. W. Etiology of Milksickness. Northwest. Med. and Surg. Jour., vol. 14, p. 156, 1857.—Townshend, N. S. Milk-Sickness. Jour. Comp. Med. and Surg., vol. 4, p. 118, 1883.—Schmidt, C. H. Milk Sickness. Cincinnati Lancet and Observer, vol. 20, p. 411, 1877.

[e] Yandell, L. P. Report on Milk Sickness. Proc. State Med. Soc. Kentucky, p. 94, 1868. [Gives negative reports.]

[f] Graff, G. B., l. c., p. 359.

[g] Crookshank, N. Observations on the Milk Sickness, Cincinnati, 1840, p. 11; Sick Stomack, Ohio Med. Rep., vol. 1, p. 11, 1826.—Yandell, L. P. Inquiry into the Nature of the Disease Called Milk-Sickness. West. Jour. Med. and Surg., 3 s., vol. 9, pp. 383, 389, 1852.—Walker, J. W. Milk-Sickness. Science, vol. 8, p. 483, 1886.—Wilkinson, G. W., l. c., p. 158.—Thompson, S. W. Milk-Sickness. West Jour. Med. and Surg., 3 s., vol. 11, p. 480, 1853.—Jones, J. T. Short Essay on Milk Sickness. East Tenn. Rec. Med. and Surg., vol. 1, p. 330, 1852–53.

[h] Jones, J. T., l. c., p. 329.

[i] Connor, J. J. Further Contribution to the Subject of Milk-Sickness. Chicago Clinic, vol. 17, p. 333, 1904.

[j] Yandell, L. P., l. c., p. 387.—Walker, J. W., l. c., 540; also Trans. Indiana State Med. Soc., 1873–75, p. 128.

NOTE.—Some areas are not entirely freed by cultivation.

[k] Yandell, L. P., l. c., p. 379.

NOTE.—J. S. Seaton in his "Treatise on the Cause of the Disease Called by the People the Milksickness," p. 10, claims that he can pick out milksick areas by the geological conditions.

[l] Drake, D., l. c., p. 184.

disease is contracted by leaving the cattle in these areas over night and that the disorder can be avoided by withdrawing them from pasture before dark.[a] Corn fodder experimentally exposed to the dew in these areas communicated the disorder to a yearling.[b]

One of the peculiarities claimed for this disease is that cows will show no symptoms so long as they are milked, while their nursing calves die with typical symptoms, but when the milking ceases the cows develop the symptoms in the usual manner. In other words, the poisonous agent is partially eliminated by the milk.[c] The urine is also claimed to eliminate a portion of the poisonous body.[d] The suspected milk in some cases was noted to be of a greenish color,[e] but usually there was no characteristic noted which is peculiar to it.[f]

The disease was apparently known to the early French missionaries in the eighteenth century, but accounts of it first appeared in medical literature in 1809–10.[g] They were numerous from 1840 to 1850, but now notices seldom appear.

The etiology of this disorder has remained in doubt, and Osler,[h] in an address before the young medical officers of the United States Army, mentions its causation as one of the many intricate problems remaining to be solved. Rewards were at one time offered by several States for the solution of this question, but these do not hold at present. Opinion has been divided as to whether "trembles," or milksickness, is of parasitic origin or due to the eating of certain plants, as *Rhus toxicodendron* or *R. venenata*,[i] *Bignonia capreolata*,

[a] Beach, W. M. Milk-Sickness. Trans. Ohio State Med. Soc., vol. 38, pp. 128, 130, 1884.—Lea, W. W. Cursory Remarks on a Disease Vulgarly Called Milk Sick. Phila. Jour. Med. and Phys. Sci., vol. 2, p. 51, 1821.—Way, J. H., l. c., p. 312.

[b] Walker, J. W., l. c., p. 483.

[c] Kimmell, J. A., l. c., pp. 50, 52.—Drake, D., l. c., pp. 198, 200.—Graff, G. B., l. c., p. 360.

[d] Graff, G. B., l. c., p. 360.

[e] McCall, A. Facts and Observations on the Milk Sickness. West. Jour. Med. and Phys. Sci., vol. 3, p. 467, 1830.

[f] Graff, G. B., l. c., p. 359.

[g] Drake, D., l. c., p. 162; also West. Jour. Med. and Phys. Sci., vol. 3, p. 482, 1830.

[h] Osler, W. Aequanimitas, 1904, p. 116.

[i] Landrum, Z. C. Rhus Toxicodendron, the Cause of Milk Sickness. Atlanta Med. and Surg. Jour., vol. 7, A, p. 1, 1861.—Chase, S. C. Cause of Milk-sickness. Chicago Med. Jour., vol. 18, p. 438, 1861.—McIlhenny, J. J. Treatise on the Disease Called the Milk-Sickness, Springfield, 1843, p. 6.—Nichols, J. H. Milk-Sickness. Clinic, Cincinnati, vol. 10, p. 26, 1876.—Brewington, W. J. Milk-Sickness. Clinic, Cincinnati, vol. 10, p. 76, 1876.—Crook, J. W. Twenty Propositions on Milk-Sickness. North-West. Med. and Surg. Jour., vol. 14, p. 491, 1857.—Jones, J. T. Short Essay on Milk Sickness (*Colica trementia*). East Tenn. Rec. Med. and Surg., vol. 1, p. 324, 1852–53.

Eupatorium ageratoides, *Lobelia inflata*, etc.[a] Graff[b] eliminated arsenic, copper, etc., as causative factors and showed that small quantities of the butter or cheese (1 ounce) or of the beef (4 ounces) obtained from animals with the "trembles," if fed to a dog three times a day, would reproduce the symptoms in forty-eight hours and cause death in from three to six days; but his inoculations failed to produce the disorder. Graff adds that the poisonous principle seems to possess the power of infinite reproduction, stating, "It will be found that each pound of flesh of that animal so destroyed will possess as active powers of destruction, and will, in its turn, serve to contaminate the whole body of another animal in the same degree." Vermilya[c] claims that he was able to reproduce the disorder by feeding *Eupatorium ageratoides* and that his experiments were corroborated by Rowe, but A. W. Bitting, of Lafayette, Ind., reported to this Department his experiments in which he fed a horse 210 pounds (105 kilos) of this fresh green plant in five days without serious effect. He also fed two lambs with 80 pounds (40 kilos) without effect. Similar experiments are reported by Drake.[d] The theory of a plant poison was emphasized, as herbivorous animals were supposed to be the first affected and from them the disease transmitted to the carnivora, although the cases do not always originate in herbivora.[e]

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[a] Jerry, W. The Plant that Causes Milk Sickness. Med. and Surg. Rep., vol. 16, p. 270, 1867.—Drake, D., l. c., pp. 213–224.—Jones, J. T., l. c., p. 324.

[b] Graff, G. B., l. c., pp. 357, 360, 362.

NOTE.—Graff says the meat is active "raw or boiled," but there is evidently some mistake, as he states on page 361 that "I boiled a large quantity of the beef in pure water for several hours, and afterwards evaporated the liquid thus obtained to the consistence of cream. Although this extract contained a large quantity of gelatinous matter, with some of the other constituents of the flesh, yet, on being given in large quantities, no perceptible effect was produced."

Compton, J. W. Milk-Sickness. Indiana Med. Reporter, vol. 2, p. 255, 1881.

[c] Ohio State Board of Agriculture, 13th Ann. Rept. for 1858, 1859, p. 673.—Barbee, J. W. Facts Relative to the Endemic Disease Called by the People of the West Milk-Sickness. Western Jour. Med. and Surg., vol. 1, p. 182, 1840.—Drake, D., l. c., p. 214.

NOTE.—The view that arsenic is the etiological factor in milk-sickness has been strenuously upheld by Seaton in his Treatise on the Cause of the Disease Called by the People the Milksickness. Louisville, 1841.

[d] Drake, D., l. c., pp. 215–217.

NOTE.—The cases described by Barbee in the Western Journal of Medicine and Surgery, vol. 1, p. 182, 1840, in which dogs were killed with decoctions of this plant, seem to be merely cases of so-called salt action.

[e] Compare Jones, J. T., l. c., p. 328.

In 1843 Heeringen,[a] and later, in 1853, Heusinger,[b] compared this disorder to anthrax, and in 1858 Wood on purely literary evidence argued the presence of "a germ."[c] Byford[d] and De Bruler[e] called attention to the fact "that it undergoes multiplication in the system" and that it lost none of its virulence by passing through four successive animals. Gardner[f] and Hessler[g] claim to have found parasites in the blood, while Philips[h] compares the organism seen by him to that met with in relapsing fever. The examinations of the blood made by Schmidt were negative.[i] Molds and mushrooms also have been claimed to be the etiological factors.[j] No one has yet reproduced the disease by injection of pure cultures of organisms.

The question thus remained in doubt, with the weight of evidence in favor of a parasitic origin, when a paper by Moseley[k] appeared. As his paper attributes the origin of this disorder to the eating of *Eupatorium ageratoides*, or white snakeroot, it was deemed advisable to analyze his evidence, as follows:

Experiment No. 1.—This consisted in feeding a cat weighing 4½ pounds (2,041 grams) with a solution made by extracting the leaves of three or four (?) plants in one pint (473 c. c.) of milk. After taking about one-half gill (59 c. c.) of this extract the animal showed tremors and dullness and was found dead in about twenty-six hours. The post-mortem examination proved to be negative. It is possible in this case that bacteria may have developed in the milk and produced poisonous compounds before feeding. This experiment was performed by Moseley's assistant and the animal was not seen by him until after death.

Experiment No. 2.—A tramp kitten of unknown history weighing 30 ounces (850.5 grams) was fed with a decoction made from one-half

[a] Heeringen, E. Discovery of the True Cause of the Disease Called by the People Trembles, or Milksickness. Louisville, 1843.

[b] Heusinger, C. F. Recherches de Path. Comp., vol. 1, p. 126, 1853.

[c] Wood, G. B., l. c., p. 465.

[d] Byford, W. H., l. c., p. 467.

[e] De Bruler, J. P., l. c., p. 209.

[f] Gardner, J. Milk-Sickness. St. Louis Med. and Surg. Jour., vol. 38, p. 290, 1880.

[g] Hessler, R. Preliminary Notes on an Almost Extinct Native Disease, Trembles or Milk-Sickness. Proc. Indiana Acad. Sci. for 1905, p. 122.

[h] Philips, W. H., l. c., p. 139.

[i] Schmidt, C. H., l. c., p. 412.

[j] Wilkinson, G. W., l. c., p. 159.—Howard, E. J. Mukosma. Indiana Jour. Med., vol. 2, p. 370, 1871.—Borland, S. Essay on the Milk Sickness, p. 27, Little Rock, 1845.—Drake, D., l. c., p. 218.—Johnson, J. M. Milk-Sickness. Atlanta Med. and Surg. Jour., vol. 7, B, p. 293, 1866. Compare also Mitchell, J. K., Five Essays.

[k] Moseley, E. L. The Cause of Trembles in Cattle, Sheep, and Horses and of Milksickness in People. Ohio Naturalist, vol. 6, pp. 463 and 477, 1906.

pound (226.8 grams) of the fresh plant and also some milk extract of the plant, more of the plant than the first (a larger cat) received. The cat was dull and showed tremors at times after the first feeding, but the appetite remained good, and eleven days later trembling could still be seen. Eighteen days later the animal was fed on the carcass of a rabbit which had died after eating the same plant (see experiment No. 6). This rabbit had died three days before the feeding of the cat began. Some tremors were seen in the cat, but it ate and continued active for three days, when it was killed. This experiment is open to the objection that nothing was known of the cat previous to the feeding, and cats often show slight tremulous movements of the cutaneous muscles. Then again, granting that the tremors were due to eating the meat, no record is made of having preserved the rabbit meat on ice, and decomposition may already have begun, and the mere presence of muscular tremors of unknown origin without the other clinical symptoms does not indicate the disease known as "trembles."

Experiment No. 3.—A cat whose previous history was not given was fed on the same carcass given to the cat referred to in experiment No. 2, and on that referred to in experiment No. 7, after it had stood two days, and the feeding was continued three days; then it was fed on a similar rabbit two days after death. This animal showed tremors and died in twenty days. The temperature of this animal rose about $2\frac{1}{4}$° F. on the third day before death. The buttocks were reported soiled, so evidently it had no marked constipation. Now, constipation is a symptom which Kimmell, Drake, Chesney, Graff, and others had previously noted in animals affected with the "trembles," and is one of the characteristics of milksickness.[a] Post-mortem examination showed two ounces of *acid* fluid in the peritoneal cavity.

Experiment No. 4.—A cat which was sick before beginning the experiment was fed with a milk extract of the plant, but only showed light symptoms (diarrhea) and "was seen to tremble only a few times and then under conditions which might probably have produced trembling without the aid of any poison." This animal was then fed on meat from one of the rabbits used in previous experiments. Moseley said that "the meat seemed to affect him more than the milk."

Experiment No. 5.—A dog was fed on an aqueous extract of the plant mixed with milk and some chopped-up plant mixed in hash and showed some trembling and weakness, but Moseley adds "he was not so different from usual except in the early morning but what all these things might have escaped notice if he had not been watched." In other words, an animal which Graff had shown to be very susceptible

[a] Chesney, J. P. Milk Sickness. St. Joseph Med. and Surg. Rep., vol. 1, p. 99, 1880.—Kimmell, J. A., l. c., p. 51.—Drake, D., l. c.; cow, p. 170; horse, p. 173; dog, p. 174.—Graff, G. B., l. c., p. 360.

to the "trembles," when fed with *Eupatorium ageratoides*, the supposed carrier of the disease, showed practically no symptoms. He then adds the remarkable report of his assistant: "While I held the dog's mouth open a friend poured the extract into the dog's mouth. The dog choked and coughed the extract into my face and mouth. I was in a room while the mixture was steeping and also on the previous evening. At 10.30 I was taken with a fit of cramps and the following day was nauseous. Several times during the three following days I had fits of trembling, always accompanying the extension of limb." In this connection it may be stated that the present writer's laboratory assistant and himself squeezed their material by hand, handled it, and made their own extracts in a rather close room without experiencing any such effects.

Experiment No. 6.—In this case 2 ounces (56.7 grams) of the snakeroot was placed in the cage with a rabbit. The rabbit died in three days. No tremors had been noted. This case can be excluded because of the absence of any accurate clinical report or histological examination, as rabbits are very apt to die of intercurrent diseases, especially coccidiosis.

Experiment No. 7.—This is of the same type as experiment No. 6, and open to the same objection. Moseley merely quotes the report of his pupil as to the presence of tremors.

Experiment No. 8.—This experiment consisted in injecting subcutaneously into a rabbit weighing 1,383 grams an aqueous extract of 3 grams of the plant. This injection was followed by tremors. Three days later the animal was fed with 2 to 3 ounces (57.7 to 85 grams) of the leaves and branches, and died in one hundred and twenty hours. There was no constipation. Moseley says, "The effects on her actions and appearance were not striking and might have escaped notice if I had not looked for them."

Experiment No. 9.—A rabbit was fed for three days with an aqueous extract of the plant. The only result noted was a "tremulous motion of the sides, with more rapid respiration." This animal was then fed with a milk extract of the plant. No constipation resulted, but the same trembling was seen, and save for a slight lessening of strength "she has seemed well."

Experiment No. 10.—This experiment consisted in feeding a milk extract of the plant, but with only slight action. A rabbit was reported to tremble after eating 67 grams of the leaves and branches of a fresh plant, but survived.

Experiment No. 11.—A young lamb weighing 40 pounds (18.14 kilos) was fed with the leaves of this plant. The animal showed trembling and died in four days, having eaten about 29 ounces (822 grams). There was no constipation. The kidneys were found to be

FLOWERING BRANCH OF WHITE SNAKEROOT (EUPATORIUM AGERATOIDES, L. F.).

much enlarged, weighing about twice as much as normal. One can form no positive opinion as to the cause of death. The enlarged kidneys, taken in connection with the history of convulsions and fluid in the peritoneal cavity, might suggest a nephritis.

Six ounces (170 grams) of the liver of this animal were fed to a cat. This cat showed merely a few tremors. A second cat also ate 6 ounces (170 grams) of the muscles but showed no tremors, and a dog after eating 4 ounces (103.4 grams) of the liver showed no symptoms save some dullness, but after feeding on the heart and spleen some tremors were noticed. None of these animals died.

These experiments, taken in the light of Graff's work, indicate that the sheep had not the disease commonly known as "trembles."

Moseley explains the lack of results in some of his experiments by the existence of a hypothetical immunity, but cases of milksickness are known not to possess immunity—in fact, one attack rather predisposes to another, so that it can not be said that Moseley has even proved *Eupatorium ageratoides* to be a poisonous plant, much less the cause of "trembles."

RECENT INVESTIGATIONS.

In the month of August, 1906, a rather serious outbreak of milksickness, or as it is frequently called in the case of stock "trembles," occurred in the vicinity of Minooka, Ill., resulting in the death of about 50 head of cattle. The office of Poisonous-Plant Investigations was asked to undertake an investigation into the cause of the trouble. In view of the fact that only plants as popularly understood are the subject of investigation by this office, only plants were studied. The widespread and popular belief that the eating of the white snakeroot (*Eupatorium ageratoides*), illustrated in Plate I, is the cause of the trouble seemed to direct the principal efforts of the investigations toward that common plant. It was found in considerable quantities in pastures in which the animals were supposed to have contracted the disease, and in a number of patches the plants had been browsed, presumably by the stock. Material from these patches, both dried and in chloroform water, was preserved for study.

EFFECT OF WHITE SNAKEROOT ON RABBITS.

EXTRACTS FROM DRY PLANT.

To prepare the material for use, 200 grams of the dry herb were extracted with cold water and the extract evaporated to the desired concentration in vacuo at about 55° C. When such an extract was fed to a rabbit weighing 4 pounds 2 ounces (1,871 grams) no symptoms were noted, either immediately or on the following day. Two days after the first dose a like quantity was again administered and no

symptoms appeared, the rabbit weighing 4 pounds 5 ounces (1,956 grams). After receiving three further doses, representing 200 grams each, in a period of five days the animal showed no symptoms of "trembles" or of suffering of any sort, the weight increasing under this treatment to 4 pounds 8 ounces (2,041 grams). The animal which had received this treatment gave normal delivery to young and made a rapid recovery, the young appearing abnormal in no respect. Thus, although the rabbit received the equivalent of 1,000 grams of the plant in a week, no symptoms of milksickness appeared and the animal steadily gained in weight.

After a rabbit weighing 4 pounds (1,814.3 grams) was injected subcutaneously in the back with an extract of 20 grams of the dried plant muscular tremors were felt in the limbs and in the masseter muscles, but recovery followed.

When a quantity of the same extract representing 40 grams was injected into a rabbit weighing 4 pounds 1 ounce (1,842.7 grams) no results followed, but an extract of 60 grams of the dried plant proved fatal in about twelve hours, the animal showing distinct tremors.

Following the injection of an aqueous extract representing 5 grams of the dried plant into a rabbit weighing 3 pounds 8 ounces (1,587.5 grams) there were no tremors and the rabbit was apparently normal, though the temperature rose 2.2 degrees F. in two hours and twenty-five minutes after the injection.

A rabbit weighing 3 pounds 12 ounces (1,700.8 grams) was injected subcutaneously with a concentrated extract representing 10 grams of dried Eupatorium and no tremors resulted, but in the two and one-half hours following the injection a fall of one-half a degree in the temperature was noted. Death followed during the night.

On increasing the quantity of extract until it represented 20 grams of the dried plant and injecting this subcutaneously, slight tremors were felt on careful examination by the hand over the hips after almost an hour and a half. An hour and forty minutes later no tremors were felt and the rabbit seemed normal. The temperature two and one-fourth hours after injection fell 2 degrees F. Death ensued during the night.

These animals had been kept under observation for two weeks preceding the experiment and had shown nothing abnormal.

EXTRACTS FROM FRESH PLANTS PRESERVED IN CHLOROFORM.

To prepare extracts from material preserved in chloroform the fresh plant was placed in a container and covered with water containing enough chloroform to prevent fermentation. When wanted for use the liquid was pressed out of the plant and concentrated in vacuo to the

proper degree. An extract representing 109 grams of the dried plant weighed after extraction (perhaps about 400 grams of the fresh plant) was given by mouth to a rabbit weighing 3 pounds 5 ounces (1,502.5 grams), but no symptoms were observed.

After a similar extract representing 127 grams of dry residue had been injected subcutaneously into the back of the same rabbit distinct tremors were shown in the hips and masseter muscles. Death followed during the night. No enlargement of the kidneys was seen.

EXTRACTS FROM ASH.

The method of preparation of extracts from ash was as follows: Ten grams of the dry herb were ashed in a platinum bowl and the ash washed into a porcelain bowl and carefully treated with acetic acid to decompose the carbonates, then evaporated to dryness and treated with water. The free acid was removed by repeated evaporation. The residue was treated with water, but not all dissolved, perhaps owing to the formation of basic salts. An emulsion consisting of the solution with the undissolved portion when injected subcutaneously produced marked tremors in the hips in rabbits after an hour and a quarter, and later in the masseter muscles. A marked acceleration of the respiration was also observed. After one and three-fourths hours the masseter muscles still twitched, but after two and one-fourth hours slight, if any, tremors were seen. No tremors were noted on the following day.

In ashing plants a large portion of the calcium-barium group will unite with the oxidized sulphur, forming insoluble sulphates, and thus be rendered inactive physiologically. Thus, trembling resulted from the injection of less of the inorganic salts than corresponds to 10 grams of the dry plant. This muscular twitching is well known to result from the hypodermic injection of certain salts (sodium, etc.), but not after administration by mouth.

An injection of a similar extract from 20 grams of the plant also produced the same result.

EFFECT OF WHITE SNAKEROOT ON CATS.

After an extract prepared from chloroform-preserved material corresponding to 50 grams of the dry plant residue was fed to a cat weighing 1 pound 8 ounces (680.3 grams), emesis followed in about fifteen minutes. When an aqueous extract corresponding to a dry plant residue of 39 grams was evaporated to 32 c. c. and 7 c. c. of this extract were fed twenty minutes after the emesis referred to and 11 c. c. were given thirty-five minutes later, urination and defecation followed promptly with renewed emesis in about ten minutes. Thirty

minutes after the administration of the last dose of extract 14 c. c. more were fed, emesis again resulting in about eight minutes, followed about fifteen minutes later by further efforts toward elimination by the intestines. Since in both dogs and cats emesis is especially easy, no especial significance is to be attached to that phase of the results. No tremors resulted and the appetite remained as usual.

In order to reduce the liability to emesis which may follow the administration of large doses, smaller quantities of the extract were given. If 7 c. c. of an extract concentrated to 32 c. c., representing a dried plant residue of 39 grams, were fed, no emesis followed for three hours. On taking a further dose of 8 c. c. the animal vomited within ten minutes. However, five minutes after this, slight movements of the skin could be seen, but these were apparently only such cutaneous movements as are commonly observed in cats. After 6 c. c. more were fed emesis soon followed. The same result followed the feeding of 11 c. c. after a period of about fifty minutes.

During the course of feeding with Eupatorium extracts as above indicated, the cat gained an ounce in weight in a week, showing normal appetite and evacuations. After four days more the weight increased about 5½ ounces (155.8 grams).

After a further interval of two weeks without treatment, when a concentrated extract representing 35 grams of plant was fed, no tremors or other abnormal symptoms were to be noted, although the animal was kept under careful observation. When, on the day following, an extract representing 65 grams was given no symptoms whatever followed other than evidence of a somewhat laxative action, and the cat continued to increase in weight. This animal gained 219 grams during the month it was kept under observation.

EFFECT OF WHITE SNAKEROOT ON DOGS.

An extract of Eupatorium representing 23 grams of the dried plant preserved in chloroform when fed to a dog kept under careful observation produced no symptoms, and the appetite remained normal; temperature before feeding, 100.6° F. When, twelve days later, a concentrated aqueous extract representing 200 grams of dried plant was given to the same dog, weighing 14 pounds 12 ounces (6,690.4 grams), having a temperature before feeding of 101° F., no symptoms resulted, the temperature after one and one-half hours registering 102° F. No symptoms appeared during observation for three more days, the weight increasing to 15 pounds 5½ ounces (6,959.8 grams). Eleven days later the weight increased to 16 pounds 15 ounces (7,682.7 grams). The animal was very playful throughout the investigation.

EFFECT OF WHITE SNAKEROOT ON SHEEP.

A lamb weighing about 25 kilos when fed 58 grams of the fresh plant showed merely some diarrheal symptoms.

EFFECT OF WHITE SNAKEROOT ON MAN.

The writer became so convinced of the harmlessness of the plant that he decided to take the plant extract himself. Four hundred grams of the fresh *Eupatorium ageratoides* were collected at Landover, Md., under the supervision of Prof. C. F. Wheeler, one of the botanists of the Department of Agriculture, and extracted carefully with water, chloroform being used as a preservative. This extract was evaporated in vacuo and made up to 154 c. c. At 11.10 a. m., September 30, 1907, 14 c. c. of this extract were taken. Seventy-four c. c. in all were taken by 1.45 p. m., without any special symptoms. The taste of the extract was exceedingly disagreeable. By 4.15 p. m. all but 40 c. c. had been taken; that is, an extract of over 300 grams. No untoward symptoms characteristic of milksickness were noted the following day; in fact, the writer never felt better.

To simulate the conditions which occur in herbivora, 100 grams of the dried plant from Illinois were digested with pepsin and pancreatin and the concentrated products taken by the writer in the period of one hour without the production of any serious symptoms.

SUMMARY.

To sum up, it certainly can not be said that it has been proved that milksickness is due to any constituent of *Eupatorium ageratoides*. The transmission of the disease by eating small quantities of meat or milk of animals sick with the "trembles" and the fact that cooked meat or boiled milk[a] does not produce this disorder point primarily rather to a parasitic origin, while the fact that *Eupatorium ageratoides*[b] is abundant in areas where the disease is not known and absent in some milksick areas[c] also indicates that the plant has no relation to the disease. If it does, it would be only an accidental carrier of some pathogenic organism.[d] According to reports, the same flora may be in the areas in which "trembles" occur as in those free from it, and milksickness is also said to occur where no vegetation grows (inclosed pens).[e] The disease also has disappeared from an area

[a] Smith, C. H. Milk Sickness. Boston Med. and Surg. Jour., vol. 77, p. 471, 1867–68.—Wood, G. B. Practice of Medicine, vol. 1, p. 465, 1858.

NOTE.—Some toxins from infected meat are not injured by boiling.

[b] Wilkinson, G. W., l. c., p. 153.—Graff, G. B., l. c., p. 361.

[c] Brewington, W. J. Milksickness. The Clinic, Cincinnati, vol. 10, p. 77, 1876.

[d] Walker, J. W., l. c., p. 483.

[e] Wilkinson, G. W., l. c., p. 153.

after simply clearing the woodland where it occurred and turning it into pasture.[a] Again, severe epidemics have occurred in winter when the foliage has disappeared, which would tend to exclude the higher, non-evergreen plants as the cause of this disorder. In fact, all the evidence in hand is against the causation of this disease by such plants, and certain analogies with cases of botulismus suggest a somewhat similar cause. If there is any truth in the statement that cattle exposed in pasture to night air especially contract the disease, this fact might suggest the more or less direct connection of some night organism as a carrier of the parasite, and certain parasites are supposed to be associated with certain localities.

Very little is known chemically of *Eupatorium ageratoides*.

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[a] Heeringen, E., l. c., p. 9.

NOTES.—A full bibliography can be found in Schuchardt, B., Die Milchkrankh. d. Nord Amerikaner, Janus, vol. 2, pp. 437, 525, 1897–98.

The most interesting experimental paper is that of Graff, while that of Drake is valuable for its fund of personal experiences as told by the settlers, and that of Schuchardt is the best literary handling of the question.

Eupatorium perfoliatum, a closely allied plant, has received some chemical attention, and a nonnitrogenous body, eupatorin, has been obtained. While the author states it will kill mice on subcutaneous injection, he fails to give the dose, and nothing can be drawn from this report as to its physiological activity.

Shamel, C. H. Eupatorin: The Active Principle of Eupatorium Perfoliatum. Am. Chem. Jour., vol. 14, p. 224, 1892.

Latin, G. Eupatorium Perfoliatum. Pharm. Jour. and Trans., 3 s., vol. 11, p. 192, 1881.

MOUNTAIN LAUREL, A POISONOUS PLANT.[a]

By Albert C. Crawford, *Pharmacologist, Poisonous-Plant Investigations.*

HISTORICAL INTRODUCTION.

Many members of the Ericaceæ, or heath family, contain principles which are injurious to man and to animals. Of these the members of the genus Kalmia especially interest us on account of their wide distribution in the United States and from the fact that many cases of poisoning in animals have been attributed to them. This genus is American in origin, but is found mainly in the Eastern States. The members of this group received their generic name in honor of Peter Kalm, but their popular name, laurel, was given on account of the resemblance of their leaves to those of the English laurel tree, a member of an entirely different family.[b] On account of the beauty and perfection of their flowers they were once proposed as a national emblem.[c]

Of these, mountain laurel (*Kalmia latifolia*), shown in Plate II, is probably the most important. North of Maryland it is usually known as mountain laurel, while south of Maryland it is sometimes known as ivy.[d] It has also received many other names, as calico bush,[e] laurel,[f] sheep laurel, mountain ivy,[g] wintergreen, great laurel,[h]

[a] The mountain laurel, *Kalmia latifolia* L., has long been recognized by many people as one of our most deadly shrubs. It is a poison fatal to live stock, especially to sheep and goats, which seem more likely than cattle and horses to browse on it. The Bureau of Plant Industry is in receipt of letters inquiring into the facts concerning its action and the methods of treating poisoned stock.

Dr. Albert C. Crawford, Pharmacologist, under the direction of Dr. Rodney H. True, Physiologist in Charge of the Poisonous-Plant Investigations of this Bureau, has given the matter laboratory study with the results here briefly stated.—B. T. Galloway, *Chief of Bureau.*

[b] Kalm, P. Travels into North America, 2d ed., vol. 1, p. 263, London, 1772.

[c] Bailey, L. H. Cyclopedia of American Horticulture, 4th ed., vol. 3, p. 854, 1906.

[d] Gronovius, J. F. Flora Virgin., pt. 2, p. 160, 1743.

[e] Coulter, S. Catalogue of Flowering Plants * * * Indigenous to Indiana. Dept. Geol. and Nat. Resources of Indiana, 24th Ann. Rept., 1899, p. 607.

[f] Gronovius, J. F., l. c., p. 160.

[g] Smith, J. E. Natural History of the Rarer Lepidopterous Insects of Georgia, vol. 1, pl. 73, 1797.

[h] Cutler, M. Account of Some of the Vegetable Productions Naturally Growing in This Part of America. Amer. Acad. Arts and Sci. Mem., vol. 1, p. 442, 1785.

American laurel,[a] wicky, rose laurel, etc. The Pennsylvania mountain laurel[b] (*Rhododendron maximum*) is a closely allied species, while in California the name mountain laurel is applied to *Oreodaphne californica*,[c] a member of the family of Lauraceæ.

Mountain laurel usually occurs as a shrub, growing from 5 to 15 feet high, but in the Blue Ridge Mountains of North Carolina it has been seen reaching to a height of 25 or 30 feet.[d]

The species extends from New Brunswick and Canada to Florida, and through the Gulf States to Louisiana and Arkansas, but is especially abundant through the Eastern States along the Allegheny Mountains, where it forms dense, impenetrable thickets.[e] In spite of the name "mountain laurel" it grows on hills and banks in the lowlands, but especially along the courses of streams. The leaves are of a tough, leathery consistency and are evergreen. The flowers, which are nearly destitute of odor, have a peculiar arrangement of their stamens, which bend over with their brown anthers projecting into pockets in the corolla,[f] so that when this flower is visited by a bee they fly back, scattering the pollen over its own stigma, and also over the insect, which then carries it to other flowers, securing cross pollination. The flowers have a waxlike appearance and vary from a white to a rose color. The wood of the mountain laurel is close grained and hard and is a substitute for boxwood, and it may be used for making handles of small tools, etc.[g] The powder covering the leaves has been used as a snuff.[h] The laurel leaves have been utilized ever since the time of the colonists as one of the evergreens for Christmas decorations.[i]

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[a] Coulter, S., l. c., p. 607.

[b] Marshall, H. Arbust. Amer., p. 127, 1785.

[c] Reports of Explorations and Surveys * * for a Railroad from the Mississippi River to the Pacific Ocean, 1853–54. Senate Doc., 2d Sess., 33d Cong., vol. 13, pt. 4, p. 133, 1856.

[d] Aaron, C. E. Our Common Poisonous Plants. Cram's Magazine, 1900, vol. 2, p. 502.

[e] Sargent, C. S. Report on the Forests of North America, 10th Census, p. 98, 1884.

[f] The details as to the historical structure of this plant will be found in the following works:

Paschkis, H. Contributions to a Closer Knowledge of Some Little-Known Leaves. Pharm. Jour. and Trans., 3d ser., vol. 12, p. 86, 1881–82. Also Zeits. d. allg. oest. Apoth.-vereines, vol. 18, p. 434, 1880.

Breitfeld, A. Der anatom. Bau d. Blätter der Rhododendroideæ in Beziehung zu ihrer systematischen Gruppirung und zur geographischen Verbreitung. Botan. Jahrb., vol. 9, p. 319, 1887–88.

Vesque, Julien. Caractères des Principales Familles Gamopétales Tirés de l'Anatomie de la Feuille. Ann. des Sci. Naturel. Botan., 7th ser., vol. 1, p. 240, 1885.

Solereder, Hans. System. Anatom. d. Dicotyledonen, 1899, p. 541–551.

[g] Emerson, G. B. Trees and Shrubs of Massachusetts, vol. 2, p. 445, 1875.

[h] Browne, D. J. Trees of America, p. 364.

[i] Kalm, P., l. c., p. 264.

FLOWERING BRANCH OF MOUNTAIN LAUREL (KALMIA LATIFOLIA, L.).

Notices of this plant occur in the early botanies[a] and books of American travel. Capt. John Smith describes, in his Generall Historie of Virginia, 1624, volume I, page 10, a "Kinde of tree like Lowrell," while Hudson in 1609 mentions "rose trees" as occurring on Cape Cod. Catesby describes it under the name Chamaedaphne foliis tini, floribus bullatis umbellatis, and says distinctly that "When cattle and sheep, by severe winters deprived of better food, feed on the leaves of these plants, a great many of them die annually."[b] The Delaware Indians are said to have used a decoction of these leaves for suicidal purposes.[c]

Public attention was especially called to this plant by Peter Kalm, the Swedish botanist, after whom Linnæus named the genus Kalmia. He described it under the name "spoon tree," because the Indians at that time made spoons of this wood. During his travels in America in 1748 he noted that calves which had eaten of the leaves became "sick, swelled, foamed at the mouth, and could hardly stand," and reported from the observations of the colonists that sheep, especially young ones, died very quickly after eating of these leaves, and that horses, oxen, and cows were made sick but seldom died, as these animals ate only small quantities of the leaves. Deer and partridges were said to feed on the leaves with impunity, and the venison from these deer was harmless to man.[d] A snake was said to have been killed by dropping a tincture of this plant on its back.[e]

John Bartram, an early American botanist, was an ardent lover of, and writer on, mountain laurel, and by him it was brought to Collinson's attention, who then introduced it into England about 1734.[f] It would seem more appropriate to have named the genus after him,[g] as his work antedated that of Kalm. During General

[a] Van der Donck, A. Vertoogh van Nieu Nederland, 1650. Translated by H. C. Murphy, 1854, p. 19.—Plukenet, L. Almagest. botan., 1769, p. 106; Almagest. botan. Mantissa, 1769, p. 49.—Gronovius, J. F., l. c., p. 160.—Linnæus, C. Spec. Plant., Ed. Willdenow, vol. 2, p. 600, 1799. Spec. Plant., vol. 1, p. 393, 1753. Amœn. Acad., vol. 3, p. 13, 1764.—Trew, C. J. Plantæ Selectæ, 1750, pl. 38. Ray, J. Hist. Plant., vol. 2, p. 1927, London, 1688. [Bannister's list of 1680.]—Hudson, H. Discourse. Collections of the New York Historical Society for the Year 1809, vol. 1, p. 121.

[b] Catesby, M. Natural History of Carolina, vol. 2, p. 98, 1743.

[c] Barton, B. S. Some Account of the Poisonous and Injurious Honey of North America. Amer. Phil. Soc. Trans., 1802, vol. 5, p. 61.

[d] Kalm, P., l. c., pp. 264–265.

[e] Barton, B. S. Collections for an Essay towards a Materia Medica of the United States, pt. 2, p. 27, 1804.

[f] Aiton, W. Hortus Kewensis, vol. 2, p. 64, 1789.—Catesby, M., l. c., p. 98.

[g] Darlington, W. Memorials of John Bartram and Humphry Marshall, pp. 130, 141, 228, etc., Philadelphia, 1849.—Bartram, John. Observations, London, 1751, pp. 26 and 69.

Braddock's campaign against the French and Indians in 1755 many horses[a] were lost from eating mountain laurel. The plant was introduced into France by Michaux.[b] In 1802 George G. Thomas[c] performed some experiments with *Kalmia latifolia* and *K. angustifolia* on himself, on a friend, and on some dogs. These experiments he embodied in an inaugural dissertation which was presented to the University of Pennsylvania. Six to 15 grains (0.4 to 1.0 gram) of the dried leaves produced distinctly unpleasant symptoms—rapid pulse, a feeling of fullness with pain in the head, throbbing of the temples, with nausea, vomiting, and dilatation of the pupils. In dogs the administration of a decoction of 30 grains (2 grams) was followed by marked salivation, with stupor, rapid respiration and purgation, paralysis, and finally convulsions. Thomas made the interesting observation that if the laurel was mixed with lard the toxic symptoms were much lessened. He examined the distillate from the leaves for an essential oil, but failed to find any.

After Thomas, several experimenters reported on the action of mountain laurel upon themselves. Bigelow,[d] who saw the dried leaves taken in doses up to 20 grains without producing symptoms, questioned if the leaves had a specific action, and traced any injurious effect they might exert to their indigestibility. Others, as Osgood,[e] Stabler,[f] and an anonymous author in the Boston Medical and Surgical Journal, volume 10, page 213, reported severe symptoms on themselves.

This action was compared with that of Veratrum.[g] From this time on few reports of experiments were published, yet the number of cases of poisoning in stock reported to the Department of Agriculture induced the Commissioner to call attention to this subject in his report of 1863.[h] Sheep are the animals usually reported as affected by the plant. Under ordinary conditions, however, eastern-bred sheep will not eat the plant unless they are starved or their supply of green or attractive food has been cut off.

As is well known, most of the cases of poisoning occur in winter,[i] when the laurel is the only green plant around, although western-bred

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[a] Barton, B. S., l. c., p. 60.

[b] Browne, D. J. Trees of America, p. 364.

[c] Thomas, G. G. Inaugural Dissertation on the Kalmia Latifolia and Angustifolia, Philadelphia, 1802.

[d] Bigelow, J. Amer. Med. Bot., vol. 1, p. 140, 1817.

[e] Bigelow, J., l. c., vol. 3, p. 185, 1820.

[f] Stabler, R. H. On Kalmia Latifolia. Amer. Jour. Pharm., n. s., vol. 10, p. 241, 1845.

[g] Medical Properties of the Kalmia Latifolia. Boston Med. and Surg. Jour., vol. 10, p. 213, 1834.

[h] Report of the Commissioner of Agriculture for 1863, p. 242.

[i] Remarkable Instance of the Absence of Animal Instinct. Penny Magazine, vol. 7, p. 283, 1838.

sheep if suddenly turned into a laurel area may eat it at any time. As the leaves are tasteless and of a tough, leathery consistency, it is very evident why animals will not eat the plant under ordinary conditions.

A good illustration of actual poisoning is given by Rusby[a] where out of a flock of 1,000 sheep which escaped into a laurel area, at least 27 showed symptoms of poisoning. Those affected were mainly the young ones. In these cases the tracks on the snow around the bushes and the presence of leaves in the stomach showed conclusively the cause of the trouble. Halsted[b] reported poisoning in cows after eating laurel wreaths which had been thrown from a cemetery into their pasture. A striking case occurred in the National Zoological Park, Washington, D. C., where six Angora goats were poisoned by laurel thrown to them by visitors; later, a Diana monkey died with typical symptoms after eating the leaves held to it by a visitor. The leaves of the plant were found in the monkey's stomach. The post-mortem examination in this case was negative. Since these poisonings occurred visitors have been prohibited from carrying laurel into the park.

Barton in 1802[c] called attention to the fact that the honey made from *Kalmia angustifolia* was poisonous to man, and while no direct proof[d] has been published that honey made from *K. latifolia* is poisonous it is perfectly logical to suppose that it is, as Plugge found that honey made from *Rhododendron ponticum*,[e] a closely related plant, gave the same chemical and physiological tests on frogs and mice which he considers characteristic of its active principle, andromedotoxin. *Rhododendron ponticum* is the plant which is supposed to have yielded the honey which poisoned Xenophon's[f] army.

Under these circumstances the Secretary of Agriculture advised against raising bees in the neighborhood of mountain laurel. An unpublished report is on file at this office of investigations in which extracts of mountain laurel were mixed with honey and fed to bees.

[a] Rusby, H. H. The Poisonous Properties of Mountain Laurel. Drug. Cir. and Chem. Gaz., vol. 46, p. 27, 1902.

[b] Halsted, B. D. Eighth Annual Report of the New Jersey Agricultural College Experiment Station for 1895, p. 355, 1896.

[c] Barton, B. S. Some Account of the Poisonous and Injurious Honey of North America. Amer. Phil. Soc. Trans., 1802, vol. 5, p. 59.

[d] American Bee Journal, 1896, pp. 92, 146, 246, 262.—Root, A. I. A B C of Bee Culture, p. 249.—Honey from Mountain Laurel. American Bee Journal, vol. 35, p. 825, 1895.

[e] Plugge, P. C. Giftiger Honig von Rhododendron ponticum. Arch. d. Pharm., vol. 229, p. 554, 1891.—Thresh, J. C. Notes on Trebizonde Honey. Pharm. Jour. and Trans., 1887–88, vol. 18, pp. 397, 404.

[f] Pliny. Nat. Hist. (Translated by Bostock and Riley), vol. 4, p. 341. Abbott, K. E. Letter, in Proc. Zoolog. Soc. London, pt. 2, p. 50, 1834.

The name of the investigator can not now be ascertained. These bees are said to have shown no symptoms, but the honey they made produced typical symptoms in two persons who ate it.[a] It has been claimed that the flesh of birds after eating laurel is poisonous to man,[b] but Wilson,[c] Audubon,[d] and Aaron[e] state that they have frequently eaten without injury partridges whose craws were filled with laurel leaves and buds. It is probable that many of these cases of poisoning were really due to ptomaines, as they usually occurred from undrawn animals.

There are few cases in man of poisoning with laurel. Children are said to have been poisoned by eating the plant in mistake for *Gaultheria procumbens*,[f] although there are no published cases to that effect. Laurel is claimed to be used in certain liquors to render them more intoxicating.[g] Barton[h] noted that the flowers of *Kalmia latifolia* would produce a vesicular eruption in certain persons.

EFFECT OF MOUNTAIN LAUREL ON SHEEP.

Stable-fed sheep and lambs were turned into an inclosed area in which the mountain laurel was the only green plant. These sheep, which were kept under observation for several hours, refused to do more than merely nibble at the leaves, and when placed in grassy areas where this plant was growing they positively refused to touch it. These observations agree with those of Wood[i] on *Kalmia angustifolia*. Other animals besides sheep seem disinclined to eat it. Kalm reported in 1754 that the leaves of the trees in Pennsylvania were devoured by a worm, but that the mountain laurel leaves were untouched.[j]

Sheep weighing about 50 pounds (25 kilos) were fed with doses of 5, 10, 15, 25, and 35 grams of the dried ground-up leaves inclosed in gelatine capsules without producing poisonous symptoms. Fifty grams, when given to a sheep weighing 33.5 kilos, induced a staggering gait and slight salivation, but doses of 85 grams would cause death in a very few hours unless diarrhea set in. Under these

[a] Unpublished answer to inquiry. See note on page 35.

[b] Barton, B. S., l. c., p. 60.—Elliot, D. G. "Game Birds" of the United States. Report of the Commissioner of Agriculture for 1864, pp. 363, 364, 1865.

[c] Wilson, A., and Bonaparte, C. L. Amer. Ornithology, vol. 2, p. 319, Edinburgh, 1831.

[d] Audubon, J. J. Birds of America, vol. 5, p. 79, 1871.

[e] Aaron, C. E. Cram's Magazine, vol. 2, p. 502, 1900.

[f] Unpublished correspondence. (G. Watkins, 1896.)

[g] Chesnut, V. K. Principal Poisonous Plants of United States. U. S. Dept. Agr., Div. Bot. Bul. 20, p. 45.

[h] Barton, B. S. Collections for an Essay Towards a Materia Medica of the United States, p. 35, 1804.

[i] Wood, T. F. Is Sheep Laurel Poisonous to Sheep? American Agriculturist, vol. 42, p. 66, 1883.

[j] Kalm, P., l. c., vol. 1, p. 266.

conditions sheep have survived this dose. In starved animals no doubt smaller doses would be poisonous.

One experiment was with a sheep about 7 years old; weight about 22.5 kilos. On June 1, 1905, at 11:05 a. m., the temperature[a] was 104.5° F., respiration 60, pulse 90 per minute. A slight secretion from the nostrils was present owing to a coryza; pupils about one-fourth of an inch wide; the conjunctival, buccal, and mucous membranes normal. Eighty-five grams of powdered dried laurel leaves in sealed gelatine capsules were given. The feeding lasted twenty-five minutes.

Following the administration of the capsules little inclination to eat was manifested, urination and slight defecation taking place during the first hour. At 1 p. m., respiration was 110 per minute, pulse 117, temperature 104° F. Marked disinclination to move was shown, the sheep permitting itself to be easily turned on its side. It ate only sparingly. Two hours after taking the laurel leaves urination was repeated and slight emesis set in, followed soon by mental dullness, as shown by decreased attention to surrounding objects, with a loss of alertness, while the face took on a sleepy appearance and saliva began to accumulate about the mouth. Respiration was somewhat labored and the unsteadiness in gait became marked. Two and three-fourths hours after eating the laurel the sheep assumed an awkward attitude in standing, the hind legs being set wide apart. Repeated emesis became a prominent feature and continued for about an hour, the ejecta being thin and mustard-like. Apparently to facilitate breathing, the mouth was kept open most of the time. Weakness and unsteadiness increased until three and one-fourth hours after eating the laurel. At this time it was difficult for the animal to stand.

At 2:46 p. m. the temperature was 107° F., respiration 50 per minute, pulse 124. The pupils were of the same size as before the feeding. The abundant nasal secretion at this time became a very marked symptom, and continued so throughout the history of the case. Weakness increased until the animal could not stand, and a diminished sensitiveness to skin irritation was noted. Death ensued quickly at 3:06 p. m. No convulsions were noted at any time.

The post-mortem examination was made at once. The sheep appeared to be well nourished. Some mustard-colored ejecta were found in the trachea as well as in the bronchioles. The lungs crepitated markedly, but showed no special amount of fluid. The pleural cavity contained no increased amount of fluid. The mucous membranes were not discolored. The heart contained no clots, was not dilated, and contained only a little dark blood. The stomach was full of food and its walls showed no signs of irritation. The intestines

[a] In all cases the temperature was taken by the rectum.

were apparently congested, but showed no hemorrhages. The small intestines were more or less filled with thin normal-looking contents. The kidneys appeared normal, the bile was of a dark-green color, and the bladder was contracted and empty. The central nervous system was not examined.

The bile from this sheep, which amounted to about 20 c. c., was treated with alcohol, and after evaporating off the alcohol in vacuo was precipitated with lead acetate. The filtrate when freed from lead by H_2S and injected into guinea pigs produced absolutely no symptoms characteristic of laurel poisoning.

On May 22, 1905, one of the yearlings previously used, weighing 24.5 kilos (49 pounds), was fed with 90 grams of powdered dried laurel leaves in sealed gelatine capsules, the feeding beginning at 11:15 a. m. and taking about fifteen minutes. Before feeding, the pulse was 135, respiration 50 per minute, rectal temperature 103.9° F. After forty-five minutes an increased secretion of saliva became evident about the mouth and the sheep nibbled slightly at the grass. At 1:15 p. m. the temperature was 105° F., the head was held low, respiration was somewhat labored, and saliva ran profusely from the mouth; pulse 104, respiration irregular, 144 per minute, pupils unchanged. Two and a quarter hours after feeding, the animal became less active, the ears were held back, and the general aspect was that of a sheep half asleep. Respiratory and salivary symptoms continued, the animal standing with the hind legs wide apart and showing evidence of weakness in the hind quarters by a staggering gait.

Four hours after feeding, profuse nasal secretion became a conspicuous feature and weakness increased to such a degree that the subject was unable to stand; respiration 120, temperature 104° F. The nostrils were moist; pupils normal. Convulsions soon appeared, with sensitiveness to touch persisting in the conjunctiva; knee jerks active, pupils a trifle dilated. Ten minutes later emesis followed. Respiration was apparently increasingly difficult. The hind legs seemed stiff. At 3:50 p. m. the pulse was 104 per minute, temperature 103.8° F., with continued attempts at emesis and repeated tossing of the head from side to side; pupils normal. Death ensued at 9:30 p. m.

No discoloration of the mucous membranes was noted, and constipation prevailed during the period of observation. At no time was a marked thirst shown. The post-mortem examination made the following day showed the trachea injected and very moist and two or three teaspoonfuls of pure serum in the pleural cavity. The lungs were œdematous. The auricles were relaxed and filled with black clots; the left ventricle contained very little black blood, while the right ventricle contained very much more. The abdomen was distended with gas. The stomach was partially filled with food; the second and third stomach walls showed no special lesions, but

the intestines throughout showed marked hemorrhagic enteritis. The small intestines contained very little solid matter, but there was some well-formed fecal matter in the cecum. The liver was perhaps a trifle pale and the kidneys were slightly injected. The spleen showed no macroscopic change. In none of these cases was it possible to secure the urine for examination, as the bladder was found empty.

On October 14, 1905, a five-year-old (?) sheep, having a temperature of 101.8° F., at 1:20 p. m. was given 90 grams of fresh laurel leaves ground up and mixed with meal. The ration was practically all eaten at 3:20 p. m., when the temperature stood at 104° F. At 6 o'clock on the next morning a failure of appetite, together with slobbering, was noted. Numerous soft stools were found in the pen during the day. At 10:12 a. m. increased salivary secretion produced a frothy appearance about the mouth and the sheep held its head low. At 2:15 p. m. slight emesis and marked secretion of nasal mucus occurred accompanied by a temperature of 103.5° F. Twenty-five hours later the slobbering had ceased, but the appetite had not returned and the temperature stood at 102.9° F. Twenty-two hours later (1:45 p. m., October 17) the temperature was 103.5° F. and the animal seemed normal. The presence in the pen of numerous soft stools was noted. The sheep recovered.

EFFECT OF MOUNTAIN LAUREL ON RABBITS.

On February 6, 1905, a rabbit weighing 2,096 grams received hypodermically one drop of aqueous extract of laurel (1 gram of dried leaves in 3.75 c. c. of water). Further administrations were made as follows: February 13, 2 drops; February 21, 3 drops; February 25, 4 drops; February 28, 6 drops; March 3, 9 drops; March 7, 12 drops; March 10, 14 drops; March 22, 20 drops. On the last date evidence of laurel action appeared and a slight loss of appetite was noted. On March 30, 25 drops were administered as before, followed on April 5 by 30 drops. At this time the animal weighed 1,828.5 grams. At 9:49 a. m. the temperature was 100.9° F., the administration of the extract following three minutes later. The resulting events were as follows: 10:05 a. m., mouth moist; 10:50 a. m., convulsions; 11:15 a. m., could not stand; 11:55 a. m., could sit up in usual posture; 1:54 p. m., appeared normal. At 3:50 p. m. the temperature was 103.3° F. The animal lived about a year after the close of this investigation.

A rabbit weighing 1,559 grams, which had not received any previous injections, was given hypodermically at 9:54 a m., April 5, 1905, 30 drops of the extract used in the preceding case. The temperature five minutes before administration was 100.8° F. The following symptoms developed rapidly: After nine minutes, interfer-

ence with the gait, followed shortly by urination and increasing evidences of weakness, with marked difficulty in standing, was noted: slight convulsions were seen 35 minutes after administration, repeated at intervals during the following hour and a quarter; at 11:15 a. m. paralysis of the hind legs led to a straddling attitude, head held back, and sphincter relaxed. The temperature at 11:50 a. m. was 95.2° F. At 1:54 p. m. the animal was much better. It could walk but staggered. At 3:49 p. m. the temperature was 102.3° F.; condition good. The rabbit seemed apparently all right until April 13, when convulsions occurred which were followed by death.

GENERAL SYMPTOMS OF POISONING.

The symptoms commonly observed are salivation, tearing, an increased flow of secretion from the nose, emesis with convulsions, and later paralysis of the limbs. On post-mortem examination the main macroscopic lesion is dilation of the vessels of the intestinal walls,[a] and if the case is not too acute, hemorrhages into the intestinal walls occur, resembling what is known as rhododendron poisoning. The aqueous extract of the flowers produced the same symptoms on rabbits as that made from the leaves.

ACTIVE PRINCIPLE.

Comparatively little chemical work has been done with mountain laurel save testing for a volatile oil[b] and arbutin.[c] Most of the chemical work has been done on a closely related plant, *Andromeda japonica*, now known as *Pieris japonica*. Eykmann[d] isolated an amorphous glucosidal body which he called asebotoxin, which melted at 120° C. and had a lethal dose for rabbits of 3 mg. per kilo. Plugge[e] studied the same plant, making his first report in 1882. He extracted the plant with water, then precipitated with lead acetate and lead subacetate, and after removing the lead with sulphureted hydrogen or sodium sulphate concentrated the fluid in vacuo at 50° C. This colorless fluid was then shaken out with chloroform, and the chloroform on evaporation left transparent, noncrystalline scales, which he called andromedotoxin. The mother liquid gave an amorphous

[a] In one case of poisoning by *Andromeda polifolia*, this was noted by Plugge. Ueber d. Vorkommen d. Andromedotoxins in Andromeda Polifolia. Arch. d. Pharm., vol. 221, p. 814, 1883.

[b] Stabler R. H. On Kalmia Latifolia. Amer. Jour. Pharm., n. s., vol. 10, p. 246.—Bullock, C. On Kalmia Latifolia. Amer. Jour. Pharm., n. s., vol. 14, p. 260, 1848.

[c] Kennedy, G. W. Arbutin in Kalmia Latifolia. Amer. Jour. Pharm., vol. 47, p. 5, 1875.

[d] Eykmann, I. F. Sur le Principe Toxique de l'Andromeda Japonica. Rec. d. Travaux Chim. des Pays-Bas, vol. 1, p. 224, 1882. Phytochem. Notizen u. einige japan. Pflanzen. Abhandl. d. Tokio Daigaku, No. 10, p. 1, 1883.

[e] Plugge, P. C. Ueber Andromedotoxin. Arch. d. Pharm., vol. 221, p. 1, 1883.

body, andromedorubrin. This andromedotoxin gave no precipitates with alkaloidal reagents and did not reduce Fehling's solution, but gave certain color reactions and produced distinct and characteristic symptoms on injection into guinea pigs and frogs -severe retching, which, however, is absent after large doses; disturbances of respiration; convulsions, and paralysis.

The characteristic color reactions are as follows:

(1) Concentrated sulphuric acid gives a dark reddish brown color and dissolves it gradually. On warming it becomes a deeper red. On dilution with water this passes into a light mulberry-red, disappearing with alkalis returning with H_2SO_4.

(2) Evaporation with dilute H_2SO_4 (1:5) on water bath causes rose-red color. If the body is pure there is no odor, but if not pure there is an odor of ericinol, due to the decomposition of ericolin, an attached body.

(3) Dilute HCl acts the same as H_2SO_4, only it gives a color more nearly violet-red.

(4) Dilute phosphoric acid, 25 per cent, gives a mulberry-red color. By this means 0.0000005 gram of andromedotoxin can be recognized.

Especial emphasis is laid on the second and fourth reactions.[a] Plugge also extended his studies to other members of this group. The first of these to be examined was *Andromeda polifolia*. He made the plausible claim that because the chloroform "shaking" from the aqueous extract freed from extraneous matter by lead gave the same color reactions and produced the same action in animals as that from *Pieris japonica* it contained the same active principle, but he admitted that this body was much less active than the andromedotoxin obtained from *Pieris japonica*. He explained this weakness as being due to the fact that the plant was grown on a different soil and that the active principle varied from that of *Pieris japonica* much as the active principle of the various species of Digitalis and Aconitum vary.[b]

In using this method with *Leucothoë catesbaei*[c] Plugge noted that the first six or seven chloroform shakings gave an amorphous residue, while the seventh to the ninth gave a white crystalline body from which he obtained the characteristic physiological action and color reactions of andromedotoxin.

From *Chamaedaphne calyculata* he obtained some crystalline deposit, but in this case from the lack of material was unable to

[a] Plugge, P. C. Vorkommen von Andromedotoxin in verschied. Ericaceen. Arch. d. Pharm., vol. 223, p. 906, 1885.

[b] Plugge, P. C. Ueber d. Vorkommen d. Andromedotoxin in Andromeda Polifolia. Arch. d. Pharm., vol. 221, p. 818, 1883.

[c] Plugge, P. C. Vorkommen von Andromedotoxin in verschied. Ericaceen. Arch. d. Pharm., vol. 223, p. 905, 1885.

positively identify it as crystalline andromedotoxin. The material obtained from this plant was less active physiologically than that obtained from *Pieris japonica*. Crystals were also obtained from *Azalea indica*.

In 1887 Plugge[a] and his pupil de Zaayer[b] made a more extended study of the andromedotoxin obtained from *Rhododendron ponticum*. They summed up the previous chemical work and studied the active principle pharmacologically. They claimed that the body shaken out by the chloroform could be precipitated from alcohol or chloroform solution by ether in the form of crystalline needles. Muto failed to obtain these needles from *Pieris japonica*, the plant Plugge first worked with. This body contained carbon, hydrogen, and oxygen, but no nitrogen, and melted at 228° to 229° C. Plugge and de Zaayer gave it the empirical formula $C_{31}H_{51}O_{10}$, although the figures for this conclusion were not exact. It was readily soluble in water and alcohol, but very slightly in ether. They stated that it was more soluble in cold than in hot water, although Plugge elsewhere states the opposite. In water, alcohol, and amyl alcohol it turns the plane of polarization to the left, while dissolved in chloroform it turns it to the right. It gives no precipitate with alkaloidal reagents. When subcutaneously injected, 0.0001 gram caused death in a frog (*Rana temporaria*) in a few hours.

This conjoint paper apparently so settled the question as to indicate that all that was necessary to determine the presence of andromedotoxin was to ascertain if the chloroform shaking from the plants gave the same physiological action and the same color reaction as that described for andromedotoxin. Plugge did this with *Kalmia latifolia* and from its action on frogs decided that the fluid extract contained one-half of 1 per cent of andromedotoxin. By this method he decided that andromedotoxin was present in the following plants:

Pieris japonica Thunb.
Andromeda polifolia L.
Leucothoë catesbaei (Walt.) Gray.
Chamaedaphne calyculata (L.) Moench.
Rhododendron grande Wight.
Rhododendron barbatum Wall.
Rhododendron fulgens Hook. f.
Rhododendron cinnabarinum Hook. f.
Rhododendron punjceum Roxb.
Rhododendron ponticum L.
Rhododendron chrysanthum L.
Rhododendron hybridum Ker.
Rhododendron falkoneri Hook. f.
Rhododendron maximum L.
Kalmia latifolia L.
Kalmia angustifolia L.
Azalea indica L.
Monotropa uniflora L.
Pieris formosa Don.
Pieris ovalifolia Don.

[a] Plugge, P. C. Ueber Andromedotoxin. Arch. d. Pharm., vol. 221, p. 12, 1883.

[b] Zaayer, H. G. de. Untersuch. ü. Andromedotoxin. Arch. f. gesam. Physiol., vol. 40, p. 480, 1887.—Plugge, P. C. Andromedotoxin. Verhandl. d. X internat. med. Cong., vol. 2, pt. 4, p. 28, 1891.

Plugge concluded that andromedotoxin was the active principle of the Ericaceæ in general.

In the case of *Rhododendron hirsutum*, Plugge[a] found that the chloroform shaking failed to produce any immediate symptoms in frogs, but three hours after injection convulsions with slight respiratory disturbance occurred, with the secretion of mucus from the mouth. These symptoms completely disappeared, differing from those of andromedotoxin. This extract gave no reactions with dilute or concentrated HCl, 25 per cent phosphoric acid, and dilute H_2SO_4. In studying the distribution of andromedotoxin, Plugge makes the interesting observation that concentrated solutions of *Erica vulgaris*, now known as *Calluna vulgaris*, injected subcutaneously into frogs cause symptoms resembling those of andromedotoxin poisoning, yet chemically no trace of this body could be found.[b]

Lasché also studied the action of extracts of *Kalmia latifolia* and *K. angustifolia* on animals, and corroborated Plugge's data, but isolated no pure body and made no chemical analysis. He used the berries in his work.[c]

Matusow,[d] while accepting the belief that andromedotoxin is the active principle of the leaves, says that the chemical reactions of the root correspond with those of andromedotoxin, except with hydrochloric acid. He claims the presence of calcium, magnesium, aluminum, manganese, and iron in the roots.

Archangelsky[e] examined another member of the Ericaceæ, the *Rhododendron chrysanthum*, a native of Siberia, and isolated a crystalline principle, rhododendrin, with the empirical formula $C_{16}H_{22}O_7$, which was inactive to frogs, and a crystalline body, rhododendrol, which acted on frogs similarly to camphor. He also claimed the presence of andromedotoxin, but did not isolate it. He examined *Rhododendron ponticum* and obtained the same color reactions and physiological reactions found by Plugge with andromedotoxin.

[a] Plugge, P. C. Andromedotoxinhaltige Ericaceen. Arch. d. Pharm., vol. 229, p. 553, 1891.

[b] Plugge, P. C. Fortgesetzte Untersuch. ü. d. Verbreit. d. Andromedotoxins in d. Familie d. Ericaceen. Arch. d. Pharm., vol. 27, p. 171, 1889.

[c] Lasché, A. J. M. Examination of Some of the Poisonous Ericaceæ of North America. Pharm. Rund., vol. 7, p. 208, 1889.

[d] Matusow, H. Analysis of the Root of Kalmia Latifolia. Amer. Jour. Pharm., vol. 69, p. 341, 1897.

[e] Archangelsky, K. Ueber Rhododendrol, Rhododendrin und Andromedotoxin. Arch. f. exper. Path. u. Pharm., vol. 46, p. 313, 1901.

Hayashi and Muto failed to obtain crystalline andromedotoxin from *Pieris japonica* by using Plugge's method.[a]

So it can not be said that the active principle from mountain laurel has been actually isolated in a pure state. Using Plugge's method, the writer failed to obtain active crystals from mountain laurel, but obtained crystals by a different method, namely, from the filtrate after ether precipitation. Plugge's principle is precipitated by ether. In no case has the writer found the ether precipitate physiologically active, and an ether extract of the crude plants possessed the toxic action of the plant. Full details as to the chemical and pharmacological investigations will be made later.

Laboratory animals, as guinea pigs and rabbits, after subcutaneous injection show tearing, retching, convulsions, and later paralysis. This physiological reaction can be used as a guide in the isolation of the active principle. Before death in males there is an ejection of semen.

REMEDIAL AGENTS.

The fact that sheep which have diarrhea have recovered from toxic doses of mountain laurel would suggest purgative treatment. Farmers very commonly administer lard in this condition, and this no doubt acts by hindering absorption. The use of lard in laurel poisoning has been substantiated by the experiments of Thomas, who found that the animals were less likely to become poisoned if lard was administered. In case vomiting and purgation do not occur, this result should be encouraged by the usual agents.[b] To induce vomiting, 60 milligrams of apomorphine hydrochlorate may be given subcutaneously and purgation may be encouraged by giving 2 to 6 ounces (60 to 180 grams) of epsom salts dissolved in water as a drench. The treatment is purely symptomatic and no true antidote is known.

It seems of interest to ascertain whether the action on the glandular secretion noted can not be obtained free from great toxicity by a change in the chemical structure of the active principle.

MEDICINAL ACTION.

Thomas treated one case of diarrhea by means of a decoction of *Kalmia latifolia*, and the leaves have also been used empirically in the treatment of certain stages of fever. Locally an ointment has

[a] Hayashi, H., and Muto, K. Ueber Athmenversuche mit einigen Giften. Arch. f. exper. Path. u. Pharm., vol. 47, p. 220, 1902.

[b] Remarkable Instance of the Absence of Animal Instinct. Penny Magazine, vol. 7, p. 283, 1838.

been employed for various forms of skin diseases, such as tinea, etc., but now it has fallen entirely out of use. A tincture is still used by homeopathic physicians.[a] The only indications for its use would be as a substitute for some member of the veratrine or aconitine family.

[a] Boericke and Tafel. Amer. Homeop. Pharm., 1896, p. 279.

NOTE.—*Kalmia angustifolia* is used by the Cree Indians as a tonic. Bul. Torrey Bot. Club, vol. 12, p. 53, 1885.

NOTE TO THE SECOND EDITION.—Since the publication of this article it has been learned that the leaves used by the experimenter referred to on page 26, footnote *a*, were examined by Prof. Victor K. Chesnut, whose card catalogue was found very useful in preparing the historical portion of this paper, and he identified them as those of oleander and not of mountain laurel.

B. P. I.—340.

RESULTS OF LOCO-WEED INVESTIGATIONS IN THE FIELD.[a]

By C. Dwight Marsh, *Expert, Poisonous-Plant Investigations.*

FIELD WORK.

The word "loco," from the Spanish, meaning crazy, has been applied for a great many years to a disease of stock and sheep in the semiarid region of the West. There has been a general belief among stockmen that the disease is caused by certain weeds known as loco weeds. The name loco weed has been applied to a large number of plants, but two are considered especially obnoxious—*Aragallus lamberti* and *Astragalus mollissimus.*

More or less desultory investigations by scientific men have been made on this subject, the general result of which has been to imply that the disease was produced by some other cause than the loco plants. The later investigations have made it seem quite probable that the cause of the disease must be sought in some other direction. The investigations here recorded were undertaken to clear up first of all the doubt concerning the source of trouble.

The first essential point was to demonstrate whether the loco weeds did or did not cause the disease. The work of the first season, the summer of 1905, accomplished this demonstration in a very satisfactory way. It was clearly proved that *Aragallus lamberti* would

[a] For many years stockmen of the plains east of the Rocky Mountains have reported great losses due to a somewhat undefined cause known as "loco." It has been estimated that the losses from this source in Colorado alone have reached the sum of a million dollars per annum. A thorough investigation of the loco problem by the Bureau of Plant Industry, both in its field and laboratory aspects, was undertaken by the office of Poisonous-Plant Investigations, under the direction of Dr. Rodney H. True, Physiologist in Charge, the field work being in the hands of Dr. C. Dwight Marsh, Expert, and the laboratory work in those of Dr. Albert C. Crawford, Pharmacologist.

The importance of the results obtained, together with the fact that the publication of the rather extensive evidence accumulated is likely to be somewhat delayed, has made it seem desirable to present at once a brief summary of the results obtained.—B. T. Galloway, *Chief of Bureau.*

poison horses, sheep, and cattle and that *Astragalus mollissimus* would poison horses. *Astragalus mollissimus* does not poison cattle because they very rarely eat it.

The work of the second season, the summer of 1906, was mainly devoted to a diagnosis of the disease. The external symptoms described by stockmen were in general corroborated. The principal symptoms are the lowered head, rough coat, slow, staggering gait, movements showing lack of muscular coordination, sometimes more or less paralytic symptoms, a generally diseased nervous system, and in the later stages of the disease extreme emaciation.

The principal pathological changes are pronounced anemia of the whole system, diseased stomach walls, and in acute cases a congested condition of the walls of the stomach, while in chronic cases there are frequently ulcers. Generally speaking, locoed cattle have ulcers in the fourth stomach. There is an excess of fluids in the various cavities of the body. This is especially noticeable in the epidural space of the spinal canal. Here the effusion is more or less organized, presenting the appearance of a gelatinous mass, which is especially abundant in the lumbar region and about the exits of the spinal nerves. In most locoed females the ovaries are found in a diseased condition.

The third stage of the work was the devising of remedial measures. This was undertaken in the summer of 1907. This work naturally had two phases, (1) attempts to eradicate the weed and (2) attempts to cure the locoed animals.

In regard to the possibility of killing the weeds, it was found that this could readily be done in the case of fenced pastures. This is especially feasible with *Astragalus mollissimus*, because it occurs in comparatively small patches. *Aragallus lamberti* has a wider distribution, but it is not at all impossible to destroy this weed when in pastures. There seems to be no way of ridding the ranges of these weeds, however.

In regard to the second phase of remedial work, it was found that locoed cattle can in most cases be cured by a course of treatment with strychnine, while locoed horses can generally be cured by a course of treatment with Fowler's solution. The animals under treatment must not be allowed to eat the loco weed and should be given not only nutritious food but, so far as possible, food with laxative properties. To this end magnesium sulphate was administered to correct the constipation which is almost universal among locoed animals. It should be noted, too, that magnesium sulphate may serve to some extent as an antidote to the poison.

It may be added, in regard to the question of immunity, that loco poisoning comes on in a slow and cumulative manner, so that there is no possibility of animals becoming immune.

LABORATORY WORK ON LOCO-WEED INVESTIGATIONS.

By Albert C. Crawford, *Pharmacologist, Poisonous-Plant Investigations.*

SUMMARY OF LABORATORY WORK.

(1) Conditions analogous to those found in locoed animals occur in portions of the world other than the United States, especially in Australia.

(2) The symptoms described in stock on the range can be reproduced in rabbits by feeding extracts of certain loco plants. Those especially referred to here under the term "loco plants" are *Astragalus mollissimus* and *Aragallus lamberti.*

(3) The production of chronic symptoms in rabbits is a crucial test of the pharmacological activity of these plants.

(4) It is the inorganic constituents, especially barium, which are responsible for this poisonous action, at least in the plants collected at Hugo, Colo.; but perhaps in future loco plants from other portions of the country may be found to have other poisonous principles.

(5) There is a close analogy between the clinical symptoms and pathological findings in barium poisoning and those resulting from feeding extracts of certain of these plants. Small doses of barium salts may be administered to rabbits without apparent effect, but suddenly acute symptoms set in analogous to those reported on the ranges.

(6) The administration of sulphates, especially epsom salts, to form insoluble barium sulphate would be the chemical antidote which would logically be inferred from the laboratory work, but of necessity these sulphates would have to be frequently administered, and their value after histological changes in the organs have occurred remains to be settled. But the treatment of acute cases of barium poisoning in man is not always successful, even when sulphates combined with symptomatic treatment are employed. The conditions under which sulphates fail to precipitate barium must be considered.

(7) Loco plants grown on certain soils are inactive pharmacologically and contain no barium. In drying certain loco plants the

barium apparently is rendered insoluble, so that it is not extracted by water, but can be extracted by digestion with the digestive ferments. To be poisonous the barium must be in such a form that it can be absorbed by the gastro-intestinal tract.

(8) In deciding whether plants are poisonous it is desirable to test not merely the aqueous or alcoholic extract, but also the extracts obtained by digesting these plants with the ferments which occur in the gastro-intestinal tract.

(9) It is important that the ash of plants, especially of those grown on uncultivated soil, as on our unirrigated plains, be examined for various metals, methods similar to those by which rocks are now analyzed by the United States Geological Survey being used.

(10) It is desirable to study various obscure chronic conditions, such as lathyrism, with reference to the inorganic constituents of the Lathyrus and other families of plants.

B. P. I.—341.

THE SOURCES OF ARSENIC IN CERTAIN SAMPLES OF DRIED HOPS.[a]

By W. W. Stockberger, *Expert, Drug-Plant Investigations.*

INTRODUCTION.

For several years considerable attention has been given in England to the question of the origin of the arsenic sometimes found there in beer.[b] Some students of the question have pointed out glucose,[c] malt,[d] and hops[e] as possible sources of this substance. The occasional detection of minute quantities of arsenic in dried hops has furthered the belief that hops should be carefully examined for traces of this undesirable substance, a view which finds partial support in some experiments made with hops dried by each of the two processes used in England.[f] In one of these, known as the "direct" process, the hops are dried over open fires and are thus exposed to all the combustion products arising therefrom. In the other, or "indirect" process, a current of pure heated air is caused to pass through the

[a] The growing and curing of hops has been a subject of investigation in the Bureau of Plant Industry during the past two years by the office of Drug-Plant Investigations, under the direction of Dr. Rodney H. True, Physiologist in Charge. The execution of the work in both field and laboratory has been chiefly in the hands of Dr. W. W. Stockberger, Expert. In connection with these investigations, that phase concerning the occurrence of arsenic in hops has been touched upon with fruitful results, which are here summarized. Since the conclusions reached have an important bearing on matters of considerable economic importance, their immediate publication is deemed desirable.—B. T. Galloway, *Chief of Bureau.*

[b] Royal Commission on Arsenical Poisoning, London, 1901–1903. Report of the Medical Officer of Health for the City of London, No. 86.

[c] Windisch, W. Wochenschr. f. Brauerei, vol. 18, p. 30, 1901.—Hantke, E. Letters on Brewing, vol. 1, pp. 16–21, 1901.—Petermann, A. Ann. Sci. Agron., vol. 2, p. 396, 1901.

[d] Chapman, A. C. Analyst, vol. 26, p. 10, 1901.—Fairley, T. Analyst, vol. 26, p. 177, 1901; Pharm. Jour., vol. 65, pp. 634, 738, 1900.

[e] Baker, J. L., and Dick, W. D. Jour. Soc. Chem. Ind., vol. 23, p. 174, 1904.

[f] Duncan, C. County Analyst's Annual Report to the Worcestershire County Council, 1905, Appendix I, pp. 22–24.

hops, which do not come into direct contact with the gases or fumes from the fires. From the experiments cited the conclusion is drawn that hops dried by the indirect process are arsenic free.[a]

It is known, however, that traces of arsenic sometimes occur in hops which have been dried by the indirect process, a condition which has been urged in England as an argument against the purchase of imported hops, thus rendering more difficult the sale abroad of those grown in the United States.

Since under the ordinary conditions of hop production in the United States there is a surplus which requires an annual exportation of a considerable portion of the crop,[b] it is highly desirable that this product be prepared in every way free from deleterious substances which would interfere with its sale and use abroad.

During a recent study of the processes of curing and sulphuring hops[c] some experiments were made to determine the most probable source of arsenical contamination. The possible sources include fuels, arsenical sprays, the soil, and sulphur both when used in the field to destroy pests and when burned under the hops on the kiln during the drying process.

Since the open-fire, or "direct," process of drying is never used in this country, and as traces of arsenic have been found in hops not treated with insecticides, only the soil and sulphur were considered in these experiments, which, though not fully complete, have yielded results of so much importance to American hop growers that they are here presented in preliminary form.

ORIGIN OF SAMPLES OF HOPS EXAMINED.

The geographical distribution of hops containing traces of arsenic was first investigated. Dry commercial samples were obtained from England, Belgium, East Prussia (Altmark), Bavaria, Bohemia (Saaz), British Columbia, New York, Wisconsin, and the Pacific coast. Upon analysis[d] small quantities of arsenic (1.5 parts to the million, or less) were detected in samples from each of the regions just mentioned. These results indicate that hops from any of the hop-growing districts of the world may contain traces of arsenic, and suggest the necessity for the thorough examination of hops whatever

[a] Duncan, C., loc. cit., p. 24.

[b] Merritt, E. Bul. 50, Bureau of Statistics, U. S. Dept. Agriculture, table 5, p. 13.

[c] Stockberger, W. W. Farmers' Bulletin No. 304, U. S. Dept. Agriculture, 1907, pp. 19–26.

[d] Except when otherwise stated all analyses for arsenic were made in the Bureau of Chemistry, United States Department of Agriculture.

their geographical origin, as well as the desirability of a careful scrutiny of the methods of cultivation and curing used abroad, particularly those processes in which, contrary to the American practice, hops are dried over open fires.

EXAMINATION OF HOP SOILS.

Samples of soil from a number of American hop fields have been examined for arsenic,[a] but in no case has its presence been detected. However, these results do not necessarily prove the absence of arsenic from the soils of the fields examined, since the hop plant has a very extensive and deep-growing root system which might very readily explore soil layers unrepresented in the samples taken.

Since traces of arsenic have been found in unsulphured hops grown on some of the soils from which these samples were taken, it may be inferred that the samples were not representative of the true soil conditions as just noted or that arsenic may be present in the soil in quantities too minute to be detected by the ordinary methods of analysis, the larger and measurable quantity in the plant being due to gradual accumulation during the process of growth.

THE ABSORPTION OF ARSENIC BY THE GROWING PLANT.

Some early authors held that living plants did not absorb arsenic,[b] but numerous plants have been found to contain this substance,[c] which was doubtless derived from the soil. Nobbe[d] states that only a very small quantity of arsenic is taken up by plants, though according to Angell[e] plants of rhubarb, bean, rye, and buckwheat accumulate appreciable quantities from soils heavily fertilized with superphosphates. Davy[f] found arsenic in peas, cabbages, and Swedish turnips grown in soils mixed with superphosphates, 10 per cent of which Lyttkins[g] states contain arsenic, in amounts varying from 0.012 to 0.26 per cent as estimated by Stoklasa.[h] Collins[i] found that barley

[a] The analysis of the soil samples was made in the Bureau of Soils, United States Department of Agriculture.

[b] Targioni-Tazzetti, A. Ann. Sci. Nat., ser. 3, vol. 5, pp. 177–191, 1846.—Danberry, Chas. Quart. Jour. Chem. Soc., vol. 14, pp. 209–230, 1862.

[c] Pfeffer, W. Pflanzenphysiologie, 2 ed., vol. 1, pp. 432–433, 1897.

[d] Nobbe, F., Baessler, P., and Will, H. Landw. Versuchstat., vol. 30, p. 409, 1884.

[e] Angell, A. and A. F. Chem. and Drug., vol. 60, p. 430, 1902.

[f] Davy, E. W. Philos. Magazine, vol. 18, pp. 108–113, 1859.

[g] Lyttkins, A. Kgl. Landw. Akad. Handl., vol. 33, pp. 317–320, 1894.

[h] Stoklasa, J. Ztschr. Landw. Versuch. Oesterr., vol. 1, p. 154, 1898.

[i] Collins, S. H. Jour. Soc. Chem. Ind., vol. 21, pp. 222–223, 1902.

grown on soils containing arsenic may accumulate large amounts of this element, most of which, as has been further shown by pot experiments,[a] occurs in the barley grains. Likewise, Gosio[b] records the accumulation of arsenic in the leaves, stems, and fruits of squash plants which had been watered with dilute arsenic solutions.

In order to test the capability of the hop plant to take up arsenic from the soil, two adjoining plats of sixty hills each were selected in a hop yard and from May 24 to August 5, 1907, the alternate hills of one plat were watered weekly with solutions of arsenious acid and those of the other with solutions of arsenic acid. Each solution was made up in five different strengths, the arsenious acid ranging from 0.01 to 1 per cent and the arsenic acid from 1 to 3 per cent. Solutions of each acid were then applied to fifteen groups of two hills each in amounts so regulated as to form a gradually increasing series. In this way the total amount of arsenious acid administered to the plants of each hill ranged from one-tenth of an ounce to 24 ounces and the arsenic acid from 2 to 20 ounces to each hill. When the hops were mature, those from each group of two hills which had received the same treatment were gathered separately, dried without sulphur, and prepared for chemical examination.

Upon analysis traces of arsenic, from 0.5 to 3 parts per million, were found in each sample examined. While the amount of arsenic in various samples was not in direct proportion to the amount administered to the plant, the balance of evidence is in that direction. Necessarily the experimental error is very large, but when due allowance is made for it the results warrant the conclusion that hops will take up from soils containing available arsenic amounts relatively proportional to the quantity contained therein.

IMPURE SULPHUR AS A SOURCE OF ARSENIC.

That the sulphur used in sulphuring hops frequently contains small quantities of arsenic is quite generally known and has been suggested as the source of the arsenic occasionally found in dried hops.[c] However, analysis of the different grades of sulphur in common use indicates that from the quantities applied in most cases sufficient arsenic would not be produced to account for the traces sometimes found in hops, provided it was uniformly distributed through them. Analysis shows that there is often wide variation in the amount of arsenic contained in samples drawn from different bales

[a] County Councils Cumberland, etc. Tech. Education Rept., vol. 10, pp. 1–121, 125–150, 1901.

[b] Gosio, B. Atti r. Accad. Lincei, vol. 15, pp. 730–731, 1906; abstract in Centbl. Bak. Par. u. Infek., part 2, vol. 18, pp. 724–725, 1907.

[c] Rüffer, E. Wochenschr. f. Brauerei, vol. 18, p. 109, 1901.

of the same lot in which all the hops were grown and dried under practically the same conditions, and also in samples drawn from different portions of one and the same bale.

This apparent contradiction may be explained on the assumption that the arsenic volatilized by the burning of the sulphur is deposited on the layers of hops next the floor of the kiln while the upper layers remain practically free. To test this theory, a series of experiments was made with a small kiln in which different lots of hops were separately exposed to the fumes of equal amounts of the different grades of sulphur, after which samples were carefully taken from the top and bottom layers before the hops were removed. The experiment was repeated with double the quantity of each grade of sulphur used before. For comparison, a certain quantity of arsenious oxid was added to the sulphur, with which a final lot was treated.

The preliminary results of these experiments fully support the theory that arsenic may be transferred from sulphur to hops and unequally distributed therein. The analysis of the samples shows in practically every case a very appreciable difference between the amounts of arsenic deposited in the upper and lower layers of the hops. The evidence further indicates that the greater portion of the arsenic is deposited in the bottom layer. The variation in the results obtained with the different grades of sulphur was less than was anticipated, since each grade apparently increased materially the arsenic content of the hops.

Although each test was repeated, using double the amount of sulphur, the relative proportion of arsenic present was not constant. However, the results indicate that a larger arsenic content may be expected when the proportion of sulphur used is increased.

The samples from the last experiment, in which arsenious oxid (the white arsenic of commerce) was added to the sulphur, contained relatively large quantities of arsenic, twelve times as much being found in the hops of the bottom layer as in those of the top layer.

CONCLUSIONS.

From the foregoing experiments the following conclusions are drawn:

(1) Traces of arsenic may occasionally be found in dried hops irrespective of their geographical origin.

(2) If available arsenic is present in the soil it may be taken up by the hop plant under favorable conditions.

(3) Except in rare cases the amount of arsenic derived from the soil by the hop plant is probably smaller than 0.01 grain per pound of dry hops, which is the smallest amount regarded as deleterious by the Royal Commission on Arsenical Poisoning in England.

(4) By the use of impure sulphur during the process of curing, hops may be contaminated with arsenic, which will be concentrated in the lower layers on the kiln floor with the result that certain samples may show an amount greater than 0.01 grain per pound.

(5) The probability of hops acquiring arsenic from what seems to be a very ready source may be much lessened by employing only the very highest grades of purified sulphur in hop curing, and the quantity used should be reduced to the lowest possible limit.

B. P. I.—342.

APPLE LEAF-SPOT CAUSED BY SPHAEROPSIS MALORUM.

By W. M. Scott, *Pathologist*, and James B. Rorer, *Assistant Pathologist*,
Investigations of Diseases of Fruits.

INTRODUCTION.

The disease of apple leaves known as "brown-spot," "frog-eye," "leaf-blight," or "leaf-spot" is very common throughout the eastern United States. As these names suggest, the disease is characterized by circular or irregular reddish brown spots with slightly raised purplish margins. (Pl. III, fig. 1.) These spots when first visible to the naked eye are very minute and purple, but rapidly increase in size until they attain a diameter of from one-eighth to one-half inch, while the affected tissue becomes brown and later sometimes gray. The mature spots are usually circular, but after midsummer may become more or less irregular or distinctly lobed in outline, a condition apparently brought about by a secondary extension of the disease from two or more points on the margin of the original circular spot. If the infection is bad, a number of spots may coalesce and form large brown patches involving half the leaf or more, but in these dead areas the margins of the individual spots usually remain distinct.

These spots should not be confused with those produced on apple leaves by the apple-blotch Phyllosticta. The latter are yellowish and minute, never more than one-sixteenth of an inch in diameter, and will not be considered in this paper.

Leaf-spot is of greater economic importance than is generally supposed. It makes its first appearance early in the spring as the leaves are unfolding, and infections take place continuously throughout the growing season. As a result of its attacks trees may become completely defoliated from six weeks to two months before the normal period of leaf fall. If this is repeated for a series of years, the trees become weakened and the life of the whole orchard is materially shortened. Moreover, the fruit from such prematurely defoliated

trees is small and of poor quality, and the fruit buds must necessarily go into the dormant stage in a rather immature condition, often resulting in a partial or complete failure of the next year's crop.

CAUSE OF LEAF-SPOT.

Considerable confusion has existed as to the cause of this leaf-spot disease. Though no inoculation experiments have been reported, the disease has generally been conceded to be of fungous origin and has commonly been attributed to *Phyllosticta pirina* Sacc., and less commonly to *Phyllosticta limitata* Pk. and *Sphaeropsis malorum* Pk., while species of Hendersonia, Pestalozzia, and other fungi have been reported as occurring on the diseased areas.

The disease in its economic aspect was first mentioned by Alwood [1a] in 1892, when he described a "brown-spot" of apple foliage and reported a serious outbreak in the Virginia orchards during the preceding summer. He attributed the trouble doubtfully to *Phyllosticta pirina*.

In 1895 Kinney [2] cited the same fungus as the cause of apple and pear leaf-spots in Rhode Island.

Stewart,[3] in 1896, reported a serious outbreak of leaf-spot on Long Island caused by an undescribed fungus which Peck named *Phyllosticta limitata*.

In 1898 Alwood [4] again recorded the common occurrence of *Phyllosticta pirina* on leaf spots, but found *Sphaeropsis malorum* Pk. and *Hendersonia mali* Thüm. associated with it.

Lamson,[5] in 1899, gave *Phyllosticta pirina* as the cause of "brown-spot" of apple foliage in New Hampshire, while Corbett,[6] in 1900, described a "brown-spot," or "frog-eye," in West Virginia due to the same fungus.

In 1902 Stewart and Eustace [7] questioned the parasitism of *Phyllosticta pirina* and *P. limitata*. In their opinion "at least a large part of the so-called apple leaf-spot is due to spray injury and weather conditions and not to fungous origin." They suggest that the fungi in question live saprophytically on leaves injured by Bordeaux mixture and arsenical sprays, or in the case of unsprayed trees on leaf-spots which are in some way the result of atmospheric influences. A possible explanation for the formation of the spots is "when a shower is followed by bright sunshine, drops of water on the leaves act as lenses and concentrate the sun's rays to such an extent as to overheat the tissues underneath."

In 1902 Clinton [8] recorded *Sphaeropsis malorum* as the cause of brownish spots on apple leaves in Illinois "much like those of the

[a] The serial numbers used in this paper refer to the bibliography, which will be found on page 54.

FIG. 1.—APPLE LEAVES SHOWING LEAF-SPOTS PRODUCED BY NATURAL INFECTION.

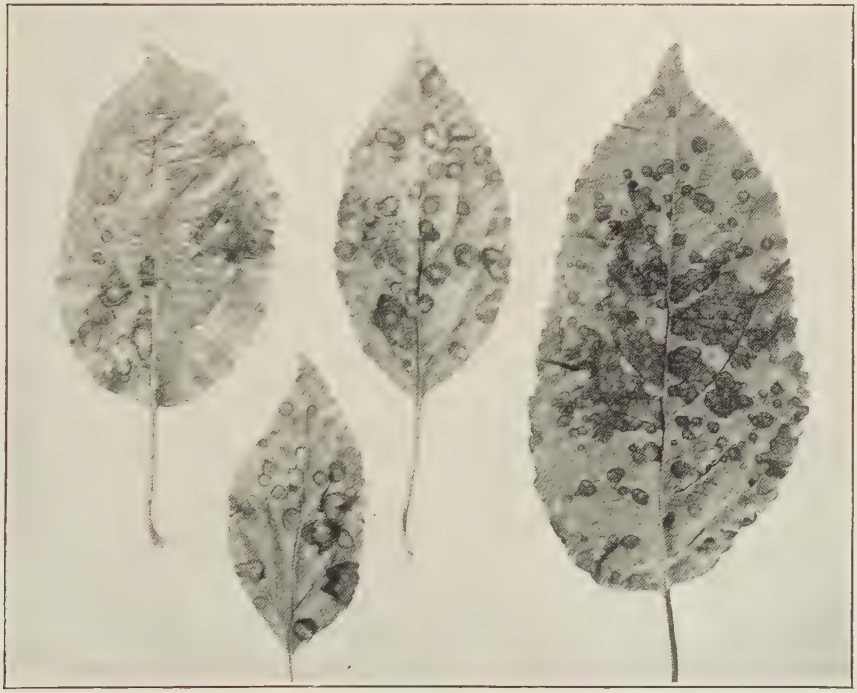

FIG. 2.—APPLE LEAVES SHOWING LEAF-SPOTS PRODUCED BY INOCULATION WITH SPHAEROPSIS MALORUM, PK.

leaf-spots or Phyllostictae fungi, but are apt to be more irregular and larger." The same author,[9] in 1903, stated that most of the apple leaf-spot troubles in Connecticut were due to this same fungus.

Stone and Smith,[10] 1903, in accounting for a serious outbreak which occurred in Massachusetts the previous year say "there can be no reasonable doubt that frost was the destructive agency." They observed that the spotting of the leaves continued throughout the summer, and that even as late as August spots as a result of spring frost developed on leaves which had not previously shown the injury.

Sheldon,[11] in 1907, transferred the fungus *Phyllosticta pirina* Sacc. to the genus Coniothyrium on account of the dark color of the spores and proposed the name *Coniothyrium pirina* (Sacc.) Sheldon. From an examination of herbarium material and fresh specimens from different parts of the eastern United States there is no doubt that the fungus commonly called *Phyllosticta pirina* in this country is a Coniothyrium. Apparently mature spores from a European specimen of *Phyllosticta pirina* in the herbarium of the Department of Agriculture are hyaline and ellipsoid, agreeing with the original description of Saccardo,[12] so that his species may prove to be autonomous.

In view of the conflicting statements and apparent uncertainty as to the cause of apple leaf-spot, the writers during the summer of 1906 and 1907 made a study of the disease in connection with demonstration spraying work in the Ozarks. It was found that *Sphaeropsis malorum*, contrary to the general belief, is the cause of the disease.

CULTURAL STUDIES.

A somewhat cursory examination of a large amount of leaf-spot material collected in Arkansas during 1906 showed that there was no one fungus which fruited constantly on the spots. The pycnidia of *Coniothyrium pirina* (Sacc.) Sheldon were found perhaps more commonly than any other, but two species of Pestalozzia and one each of Coryneum, Hendersonia, and Alternaria occurred frequently, while occasionally the pycnidia of *Sphaeropsis malorum* and a species of Septoria were met with. The same was true of specimens received from Missouri, Nebraska, New York, Maryland, Virginia, and West Virginia. Pure cultures of all of these fungi were easily obtained by the poured-plate method. All grew well and fruited abundantly on apple agar or sterilized apple wood.

In the early part of the season of 1907 cultures were obtained from leaf spots by a somewhat different method. During the first spring outbreak of the disease, spots of various sizes, together with a little of the surrounding healthy tissue, were cut from the leaf and placed in a solution of mercuric chlorid (1–1,000) for two or three minutes. The bits of leaf were then thoroughly washed in sterile water and

transferred to slanted apple or potato agar. The writers separately made many sets of cultures by this method, using spots from leaves of Ben Davis, Winesap, and White Pearmain trees. Within a few days by the aid of a hand lens hyphæ could be seen growing out from the center or margins of the small spots. Mycelium developed rapidly and in about two weeks spores were formed, so that the fungi could be identified. The results were uniformly the same. In all cases in which the youngest spots, that is, those one-sixteenth of an inch or less in diameter, were used, the fungous growth was a pure culture of *Sphaeropsis malorum* Pk. In cultures made from the older spots, in which the central tissue had become brown, sometimes a pure Sphaeropsis was obtained, but more often a mixture of things. *Coniothyrium pirina* developed about as commonly as Sphaeropsis, both species often growing from the same spot. In addition to these two fungi, two species of Alternaria, a Cladosporium, bacteria, and yeasts were frequently present.

This cultural work, frequently repeated, gave evidence that *Sphaeropsis malorum*, always developing from the youngest spots, was the specific cause of the disease and that the other organisms were mere concomitants. Of course, to prove this inoculation experiments were necessary. These were made as soon as pure fruiting cultures of the different fungi were obtained.

INOCULATION EXPERIMENTS.

A number of different sets of inoculations were made, but the method of procedure was the same in each case. With a sterile needle the fruiting fungus was scraped from the surface of the agar and transferred to a tube of sterile water. In cases where pycnidia were present these were crushed against the side of the tube with a sterile glass rod to set free the spores. In order to ascertain the presence of mature spores a hanging drop of the fluid was always examined microscopically. This spore-bearing liquid was then sprayed on both surfaces of clean young leaves with an atomizer. Trees in more or less isolated young orchards were selected, and no two fungi were used on the same tree. From 20 to 40 leaves on two or three different shoots were involved in each inoculation. Checks were always made on separate trees by spraying 40 or 50 leaves with sterile water.

The first inoculations were made on May 28, 1907. The fungi used were *Sphaeropsis malorum*, and the undetermined species of Coryneum, Hendersonia, and Alternaria previously mentioned. It was raining at the time and the weather continued wet for several days.

On June 3, 1907, purple specks were appearing on the leaves which had been inoculated with Sphaeropsis, and on June 18 these leaves were badly affected with leaf-spot. (Pl. III, fig. 2.) On a twig bearing 30 leaves, 12 showed a dozen or more well-developed spots, and a few of these leaves had from 80 to 90 spots each. Twelve other leaves on the same branch had from 2 to 10 spots each, while only 6 remained free from the disease. On another branch 12 out of 20 leaves were badly affected.

With the exception of an occasional spot, evidently resulting from natural infection, the leaves sprayed with spores of the other fungi, as well as those sprayed with sterile water as a check, remained free from the disease.

Another experiment was made on June 19, 1907. Spores of *Sphaeropsis malorum*, *Coniothyrium pirina*, Coryneum, and Alternaria were used. The work was done at sunset following a shower, so that the leaves were wet. Again the leaves inoculated with the spores of *Sphaeropsis malorum* soon became badly affected with the characteristic leaf-spot disease, while the others, including the checks, developed no more than an occasional spot.

Another test was made with Sphaeropsis alone. The young leaves of a 2-year-old tree were inoculated during a period of dry weather in mid-June. The spores were sprayed on the leaves at about 10 o'clock, while the sun was shining brightly. At the same time sterile water was sprayed on the leaves of an adjacent tree as a check. Though no rain fell for at least six days after the spraying was done, numerous purple specks began to appear on the inoculated leaves within a week and soon developed into the characteristic brown spots. A few spots, never more than one to a leaf, appeared on the checks. The mature spores of Sphaeropsis germinate so rapidly that in dry weather the dews provide sufficient moisture for leaf infection, as indicated by this experiment.

Inoculations made on June 26, 1907, with *Sphaeropsis malorum*, Coryneum, and Alternaria gave results similar to those previously recorded for these fungi. From 20 to 50 spots developed on each of the leaves inoculated with Sphaeropsis, while only a few scattered spots occurred on the leaves of the check and on those sprayed with spores of the other fungi.

On August 4, 1907, inoculations with Coniothyrium were again tried. Leaves on rapidly growing 2-year-old Ben Davis trees in a nursery were used. The spores were obtained from a fresh culture and were so numerous that they clouded the liquid. The work was done during a light shower and some rain fell the next day.

The same experiment was repeated on the evening of August 11, 1907. Though it did not rain at this time the trees were wet down with sterile water on the following night.

Again, on August 21, 1907, this same fungus was used for inoculations, which were made in the evening just after a heavy rain. For the next two days the sky was overcast and occasional showers fell.

The results of these three sets of inoculations with Coniothyrium were negative. Spots were found here and there on the inoculated leaves, but no more than on the checks which were sprayed with sterile water. Similar spots, never more than two to a leaf, were found throughout the nursery at this time and were evidently produced by a natural infection with Sphaeropsis.

CONCLUSIONS.

The following conclusions may be drawn from the results of the inoculation experiments described in the preceding pages:

Sphaeropsis malorum Pk., the black-rot fungus, is parasitic on apple leaves, producing circular (or irregular) reddish brown spots an eighth of an inch or more in diameter, and is undoubtedly the cause of the apple leaf-spot disease which occurs in the middle West. The common apple leaf-spot disease of the Eastern States, being so similar in every respect, is doubtless caused by the same fungus, although some other fungi may possibly produce similar spots.

Coniothyrium pirina (Sacc.) Sheldon, although it occurs abundantly on apple leaf-spots, appears to have nothing to do with their formation.

The several other fungi that were tested, such as *Hendersonia* sp., *Coryneum* sp., *Pestalozzia* sp., and *Alternaria* sp., proved to be nonparasitic in these experiments and probably occur on leaf spots only as saprophytes.

SOURCE OF INFECTION.

Sphaeropsis malorum is perhaps the most common fungus that inhabits pome-fruit orchards east of the Rocky Mountains. It is the cause of the black-rot of the apple, the pear, and the quince and produces cankers on trunks and branches of these fruit trees. It occurs abundantly on dead twigs and branches in nearly every orchard, producing spores in enormous numbers. This is perhaps the most fertile source of infection for both fruit and foliage. In old orchards, particularly where pruning is neglected, the leaf-spot disease is much worse than in young orchards. The leaves of young trees adjacent to an old orchard become more spotted with the disease than those farther removed. Another source of infection is the diseased fruits of the previous year's crop. Although the fungus fruits only sparingly on leaves on the tree, it produces fertile pycnidia in considerable numbers on these leaves after they have fallen to the ground.

FIG. 1.—UNSPRAYED WINESAP TREES DEFOLIATED BY THE LEAF-SPOT DISEASE.

FIG. 2.—SPRAYED WINESAP TREES IN FULL FOLIAGE, LOCATED IN THE SAME ORCHARD AND PHOTOGRAPHED AT THE SAME TIME (OCTOBER 19, 1906) AS THOSE SHOWN IN FIGURE 1.

TREATMENT.

Since 1892, when Alwood [13] first recommended Bordeaux mixture as a preventive for apple leaf-spot, other writers have advocated the same method of treatment. The prevention of this disease has been one of the most striking results of various spraying experiments and demonstrations conducted by the Bureau of Plant Industry. Waite, in 1901, in connection with bitter-rot experiments in Virginia, controlled the disease with two applications of Bordeaux mixture. His recommendations in Farmers' Bulletin No. 243, p. 19, are based upon this work. Similar results were obtained by Scott [14] in Virginia in 1905. In the spraying demonstrations in the Ozarks during 1906 and 1907 the writers found that the spraying ordinarily necessary for the protection of the fruit from fungous attacks [a] will usually control this leaf trouble without any additional treatment. During both seasons unsprayed trees were shedding their leaves by August 1 and were completely defoliated by the middle of September, while the sprayed trees remained in full foliage until the first killing frost. (Compare Pl. IV, figs. 1 and 2.) In addition to the injurious effect upon the trees this premature defoliation caused the fruit to be small and of poor quality as compared with that from sprayed trees. An average barrel of Winesaps from sprayed trees contained 612 apples, while 731 from unsprayed trees in adjacent rows were required to fill a barrel.

For the control of this disease alone, without reference to the diseases of the fruit, an application of Bordeaux mixture should be made in the spring a week or ten days after the petals have fallen, a second application four weeks later, and a third about four weeks after the second. Three applications are necessary only in exceedingly wet seasons in sections where the disease is severe. Ordinarily two treatments, one about three weeks after the petals are off and the other four or five weeks later, are sufficient.

A weak Bordeaux mixture, such as 3 pounds of copper sulphate and 3 pounds of lime to 50 gallons of water, is effective in controlling this disease, Bordeaux mixture of full strength not being required. [b]

[a] For a combination treatment for the leaf-spot disease, the diseases of the fruit, and the codling moth, see Farmers' Bulletin No. 283, pp. 41–42.

[b] For various formulas and methods of preparing Bordeaux mixture, see Farmers' Bulletin No. 243, pp. 5–10.

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B. P. I.—347.

THE IMMUNITY OF THE JAPANESE CHESTNUT TO THE BARK DISEASE.

By Haven Metcalf, *Pathologist in Charge of the Laboratory of Forest Pathology.*

THE EXTENT OF THE BARK DISEASE.

The bark disease of the chestnut, caused by the fungus *Diaporthe parasitica* Murrill, has spread rapidly from Long Island, where it was first observed, and is now reported from Connecticut, Massachusetts, Vermont, New York as far north as Poughkeepsie, New Jersey, Pennsylvania, and possibly Delaware. It is no exaggeration to say that it is at present the most threatening forest-tree disease in America. Unless something now unforeseen occurs to check its spread, the complete destruction of the chestnut orchards and forests of the country, or at least of the Atlantic States, is only a question of a few years' time.

AN IMMUNE VARIETY.

Observations made by the writer during the past year indicate that all varieties and species of the genus Castanea are subject to the disease except the Japanese varieties (*Castanea crenata* Sieb. and Zucc.). All of the latter that have been observed in the field or tested by inoculations have been found immune. This fact can hardly fail to be of fundamental importance to the future of chestnut nut culture. Although the nuts are distinctly inferior in flavor to the European varieties, such as Paragon, the Japanese chestnut is already grown on a large scale as a nut-producing tree. There are, however, many trade varieties of dubious origin. Some of these may prove later to be subject to the disease. Immunity tests of all known varieties of chestnuts have been undertaken.

Attempts will also be made to hybridize the Japanese with American and European varieties, with the hope of combining the immunity of the former with the desirable qualities of the latter.

However excellent as a nut and ornamental tree, the value of the Japanese chestnut as a forest tree is doubtful. It can be recommended only experimentally at present for forest planting. It

certainly will not take the place of the American chestnut. The tree is said to attain a height of 50 or 60 feet in Japan. As seen in this country it is a handsome tree, dwarfish and compact in habit, and rather slow growing. It has hardly had time to show how large it can grow.

The immunity of the Japanese chestnut, together with the fact that it was first introduced and cultivated on Long Island and in the very locality from which the disease appears to have spread, suggests the interesting hypothesis that the disease was introduced from Japan. So far, however, no facts have been adduced to substantiate this view.

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